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Organocatalytic CS_2 insertion into epoxides in neat conditions: a straightforward approach for the efficient synthesis of Di- and tri-thiocarbonates†

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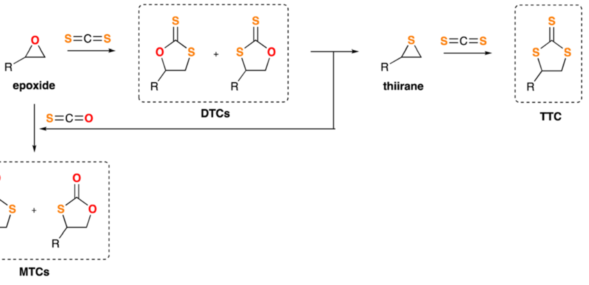
The straightforward organocatalytic insertion of carbon disulfide (CS_2) into epoxides using either choline chloride (*ChCl*) or tetrabutylammonium chloride (TBACl) is reported, for the first time, under solvent-free (neat) conditions. Fine-tuning of our system allowed us to obtain either dithiocarbonates (DTCs) or trithiocarbonates (TTCs) with high efficiency. Additionally, a mechanistic proposal is presented, supported by experimental evidence, DFT calculations and wavefunction analyses.

C1 heterocumulenes [X=C=X (*e.g.*, CO_2, CS_2, carbodiimides) or X=C=Y (*e.g.*, isocyanates, thioisocyanates, ketenes)] are versatile building blocks for creating complex organic structures with diverse properties.[1] While CO_2 chemistry is well-studied,[2] its heavier analogue CS_2 has been less explored.[3] For example, the insertion of CS_2 into epoxides to form dithiocarbonates (DTCs) or trithiocarbonates (TTCs) remains limited, despite their interesting applications, partly due to challenges in controlling chemo- and regioselectivity, which often lead to complex product mixtures (Scheme 1).[4] Although this highly-challenging reaction can be chemically domesticated, this often requires sophisticated metal-based catalysts.[5] Additionally, these CS_2 insertion reactions typically use volatile organic compounds (*VOCs*) as solvents, which are toxic, flammable, and sometimes carcinogenic.[6] Moreover, these non-renewable *VOCs* also contribute significantly to waste generation in this process.[7] Considering all these precedents, and aiming for the development of new sustainable methodologies suitable for the fixation and valorisation of heterocumulenes under the *Green Chemistry* framework,[8] herein we report the use of simple, easily-available and cheap organocatalysts for the insertion of CS_2 into epoxides. This protocol renders in demand either DTCs or TTCs, in high yields. Going one step further, and bearing in mind the phrase (coined by P. T. Anastas and J. C. Warner, usually considered the fathers of the *Green Chemistry* concept): "*The best solvent is no solvent*",[9] we describe a "*solventless*" protocol (neat conditions) without needing *VOC*-based reaction media. Finally, and aside from the *Green Chemistry* point of view, we also make special emphasis on shedding light on the mechanism of our CS_2 insertion into epoxides.

Based on literature precedents and its analogy to our previous CO_2 insertion protocol,[8a] we chose commercially available styrene oxide (**1a**) as the model substrate. Thus, **1a** was initially dissolved in CS_2, treated with a suitable organocatalyst, and subsequently heated up inside a sealed tube under vigorous stirring. After carefully scrutinising all the experimental parameters affecting the course of this transformation (see the ESI† file for details), we were delighted to find an optimised set of conditions. It implies the use of readily available and cheap choline chloride (*ChCl*, which is a biorenewable salt formerly known as vitamin B4)[10,11] or tetrabutylammonium chloride (TBACl) as organocatalysts, and 3 equiv. of CS_2 at 100 °C, for 24 hours in the absence of any external *VOC*-solvent.[12] By using



Scheme 1 General sequence for the preparation of dithiocarbonates (DTCs) or trithiocarbonates (TTCs).

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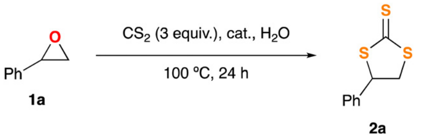
† Electronic supplementary information (ESI) available: Full experimental details, NMR spectra and computational details. CCDC 2386775–2386777. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4cc05154h

Table 1 Optimum conditions for the synthesis of trithiocarbonate **2a**[a]



Entry	Cat. (mol%)	H_2O (equiv.)	Conversion[b] (%)
1	*ChCl* (2.5)	2	93[c]
2	TBACl (10)	1	84[d]

[a] General conditions: styrene oxide **1a** (0.88 mmol) was dissolved in CS_2 and treated with an aqueous solution of the stated catalyst. The mixture was stirred at 100 °C for 24 h, inside a 10 mL sealed tube. [b] Conversion of styrene oxide into product **2a**, as determined by ^1H NMR spectroscopy from crude reaction mixtures, using $CHBr_3$ as an internal standard. [c] 5% of a corresponding monothiocarbonate (**5a**, a single isomer) was identified. [d] 7% of a corresponding monothiocarbonate (**5a**, a single isomer) was identified.

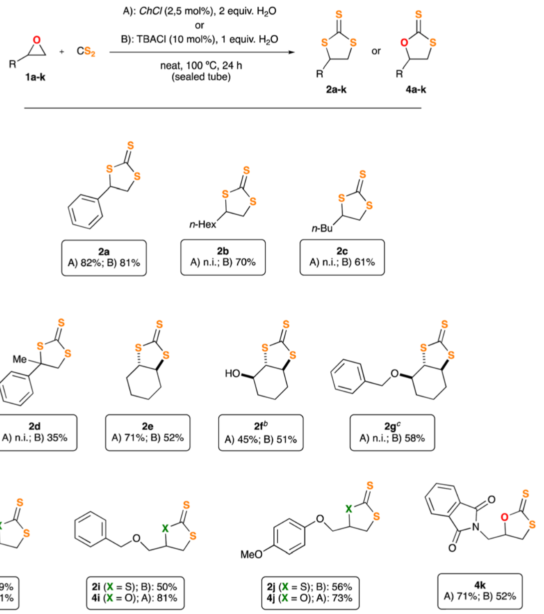
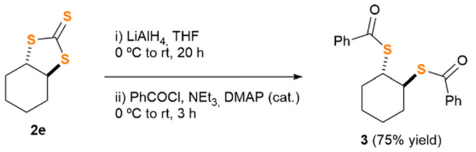


Fig. 1 Scope of the insertion of CS_2 into epoxides. [a] General conditions: epoxide **1a–k** (0.88 mmol) was dissolved in CS_2 (201 mg, 159 μL, 2.64 mmol) and treated with an aqueous solution of the stated catalyst, *ChCl* or TBACl. Reaction mixtures were stirred at 100 °C for 24 h, inside a 10 mL sealed tube. The yield of analytically pure products, purified by flash chromatography, is given. [b] (1R*,2R*,6S*)-7-oxabicyclo[4.1.0]heptan-2-ol was employed as the starting material. [c] *O*-benzyl-(1S*,2R*,6S*)-7-oxabicyclo[4.1.0]heptan-2-ol was employed as the starting material.

this simple and straightforward methodology we were able to afford the corresponding TTC **2a** in 93% conversion (in the case of using *ChCl* as the catalyst; Table 1, entry 1), or 84% (when using TBACl; Table 1, entry 2). Interestingly, we observed experimentally that the presence of water was necessary to achieve optimum results, as the chloride salts are sparingly soluble in CS_2. At this point, and in the framework of *Green Chemistry*, it is important to highlight the environmentally benign character of our protocol as: (i) it occurs under neat conditions (using CS_2 as both the reagent and the reaction media); (ii) exhibits a significant atom economy,[13] moreover when the transformation **1a** → **2a** (formation of the TTC) requires two equiv. of CS_2; and (iii) employs an organocatalytic method (as assessed by Rothenberg "*Catalysis is the key for sustainability*"),[14] in which simple, non-toxic and cheap ammonium salts (*ChCl* or TBACl) are employed as readily available off-the-bench catalysts. Going one step further, we decided to critically evaluate the sustainability virtues of our transformation by using Sheldon's *E*-factor as *Green Chemistry Metric*.[15] In this sense, and taking into account that a remarkably 86% yield of **2a** was achieved when water was the only material used for the workup of the reaction and the subsequent purification steps, we calculated an *E*-factor of 0.945, in between the range of values calculated for previous syntheses of TTCs in neat conditions (0.48 to 6.87; see ESI†).

Motivated by our preliminary results, which indicate the possibility of synthesising the desired thiocarbonates under more sustainable reaction conditions, we next decided to explore the scope and limitations of our insertion of CS_2 into epoxides. Accordingly, we selected some starting materials **1b–k**, decorated with different functional groups and structural patterns, particularly those which proved to be a challenge for other methodologies previously communicated.[4,5] Epoxides **1b–k** were subjected to the conditions described in Table 1, employing, in turns, either *ChCl* or TBACl as organocatalysts (Fig. 1). As previously observed for **1a**, all the reactions proceeded smoothly. To our surprise, their outcome relies deeply on the nature of the organocatalyst employed. Epoxides **1b** and **c** (which bear a single non-bulky alkyl substituent), afforded the corresponding TTCs **2b** and **c** in good yield when using TBACl as organocatalyst, while no reaction was observed for the case of *ChCl*. Likely, sterically encumbered epoxides **1d–g** rendered TTCs **2d–g** in moderate yield upon reaction with TBACl, being *ChCl* a superior organocatalyst for epoxide **2e**. Remarkably, products **2f** and **g** were formed in a diastereo pure form, retaining in both cases the relative spatial configuration of the stereocenter adjacent to the oxirane function. Moreover, and to the best of our knowledge, this is the first occasion in which epoxides **1f** and **g** are transformed into TTCs by either methodology.[4,5] The relative stereochemistry of products **2f** and **2g** was unambiguously disclosed by single crystal X-ray diffraction techniques (Fig. S54 and S55, ESI†). Moreover, and trying to show the importance of trithiocarbonates as building blocks for the synthesis of other organic architectures,[1] we designed a two-step synthetic protocol to convert TTC **2e** into the corresponding diastereopure bis-thioester **3** (see Scheme 2, and ESI† for details). Compound **3** was fully characterised and its relative



Scheme 2 Synthetic scheme for the derivatisation of TTC **2e** into bis-thioester **3**.

spatial configuration unveiled by single crystal X-ray diffraction analyses, which ultimately allowed us to confirm the stereochemistry of TTC **2e** (see ESI† for details).

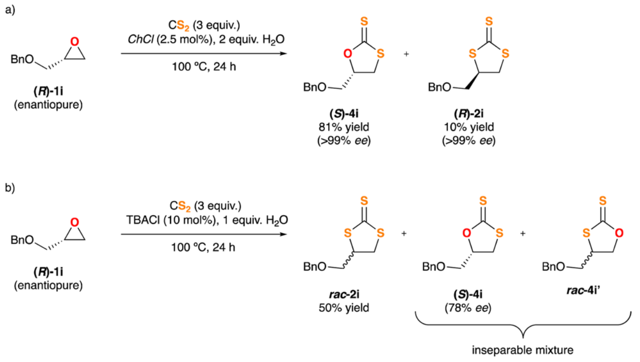
For the epoxides consisting in *O*-substituted glycidol (**1h–j**), we observed, as it was expected, the formation of the corresponding TTCs **2h–j** when using TBACl as catalyst. Importantly, and showcasing the versatility of our synthetic approach, we were delighted to find that simply replacing TBACl by *ChCl* (under the same reaction conditions and using the same starting materials), allowed us to obtain the corresponding dithiocarbonates (DTCs **4h–j**). These were isolated in good yield and without contamination from their regioisomeric forms, which is relevant for future synthetic application, as the different regioisomers cannot be separated by standard chromatographic techniques. Last, but not least, epoxide **1k**, featuring an phthalimide residue, could not be converted into the corresponding TTC, but alternatively its DTC **4k** was isolated in good yield, better when *ChCl* was used.

Based on the aforementioned experimental findings and intrigued by the various reaction pathways observed in the insertion of CS_2 into epoxides, which are strongly depending on the nature of the chloride salt used as the catalyst, next we decided to explore the behaviour of an enantiopure substrate, **(*R*)-1i**, under the optimised reaction conditions. The resulting crude mixtures were carefully purified by flash chromatography and all the fractions were characterised and analysed by HPLC using a chiral stationary phase. When TBACl was used as the catalyst TTC ***rac*-2i** was isolated as the major product, thus jeopardizing the stereochemical integrity of the substrate. Also, the DTCs mixture **4i** + **4i′** was isolated and identified. **4i** showed an erosion of its stereoinformation, while **4i′** was rendered in racemic form (Scheme 3b). In turn, *ChCl* gave rise to DTC **(S)-4i** in enantiopure form (> 99% ee) and as a single regioisomer. In this last case the stereogenic carbon of epoxide **1i** retains its configuration fully. Moreover, some TTC **(*R*)-2i** was also isolated, also in an enatiopure form, implying an inversion of configuration on the pristine stereogenic center (Scheme 3a).

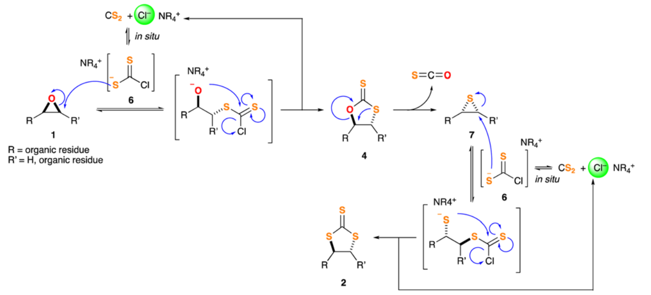
With all the above information in hand we propose the following sequence as a tentative mechanism for our insertion of CS_2 into epoxides (Schemes 4 and 5), fully supported by DFT calculations (see Appendix for details). Initially, a $[CS_2{\cdot}Cl]^-$ adduct, **6**, is formed *in situ* in the reaction medium, as it has been previously postulated.[16] It originates from the attack of the halide anion of the catalyst to the electron-cumbered sp carbon of CS_2, and would explain the effectiveness of chloride respect to bulkier bromide or iodide ions (see Table S4, ESI†). This short-lived reactive specie, highly nucleophilic, undergoes a S_N2-type addition on epoxide **1** from the downward side, opposite to the O atom. This is further supported by wavefunction analysis, which shows ideal electron delocalization values of 0.5 electron pairs at the transition stated, with the corresponding C–S and C–O bonds forming and breaking in a fully concerted and synchronous manner (Appendix Tables S10–S13, and S19–S22, ESI†). Eventually it gives rise to the corresponding DTC **4**. The latest, upon vigorous heating, extrudes S═C═O to afford thiirane **7**, which features an inversion of its stereogenic carbons.[17] Another attack of adduct **6** on thiirane **7**, again by means of a downward-facing S_N2-type process (Appendix Tables S28–S31, and S37–S40, ESI†), leads to the formation of TTC **2**.[18] Overall, this manifold explains the stereochemical outcome observed for the CS_2 insertion on cyclohexene oxide derivatives **1e–g** (Scheme 4).

The distinct reactivity of TBACl and *ChCl* is manifested on the results highlighted in Scheme 3, where the CS_2 insertion is carried out on the enantiopure substrate **(*R*)-1i**. Based on the experimental observations and the computational analysis we believe that *ChCl* follows the mechanism of Scheme 4, as the chirality of the substrate is transferred entirely to the reaction products **(*S*)-4i** (major) and **(*R*)-2i** (minor). On the contrary, the use of TBACl as the catalyst leads to a collection of products that lack any chirality, or it has been severely damaged. This experimental fact can be rationalised from the proposal outlined in Scheme 5.

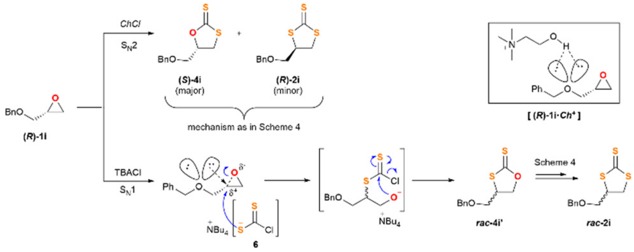
In substrate **(*R*)-1i**, the lone pairs of electrons placed on the oxygen atom bearing the benzyl substituent can assist the opening of the epoxide function. Thus, we suggest **(*R*)-1i** coexisting with a subsequent flat non-classic carbocationic-type structure, which upon reaction with nucleophile **6** leads to products ***rac*-4i′** and ***rac*-2**. It is important to note that this route does only occur when using TBACl as the catalyst, and not *ChCl*. It therefore implies that the cation accompanying the chloride ion plays a crucial role in the reaction outcome. We suggest that the choline cation can participate in a H-bonding network that comprises the electronic lone pairs of the epoxide and make them unavailable for the aforementioned anchimeric



Scheme 3 Study of the sterochemical outcome of the insertion reaction of CS_2 into chiral epoxide **(*R*)-1i**.



Scheme 4 General mechanistic proposal for the insertion of CS_2 into epoxides **1** catalysed by chloride anions.



Scheme 5 General mechanistic proposal for the insertion of CS_2 into epoxide **(*R*)-1i**, which explains the unalike outcome of the reaction when TBACl or *ChCl* are used as catalysts.

assistance (complex **[(*R*)-1i·Ch]**$^+$ in Scheme 5). Notwithstanding with this suggestion, we strongly believe that the extrusion-insertion of SCO[17] and CS_2[18] on substrates **4** and **7**, respectively, takes place simultaneously and in a quasi-reversible way, as such, it has to be considered if a full picture of the mechanism is pursued.

In conclusion, and edging closer towards the development of a straightforward, more sustainable and solventless-compatible organocatalysed synthesis of di- and tri-thiocarbonates, our experimental findings have uncovered the potential of using simple, readily available and non-toxic quaternary ammonium salts as catalysts to chemically domesticate the highly-challenging insertion of CS_2 into epoxides. Fine-tune selection of the catalysts employed (TBACl or *ChCl*), and the epoxide used as starting material allows the design of "*a la carte*" synthetic protocols for the formation of di- and tri-thiocarbonates in demand. Also, mechanistic investigations have been disclosed through reactivity studies along with electron population.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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12 Notably, we found that reducing the amount of CS_2 from 6 to 3 equivalents maintained process activity while improving atom economy and reducing waste (see ESI†).

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17 The DFT analysis shows that the extrusion of SCO from DTC **4** is, particularly, a reversible process (Appendix: Fig. S1 and S2, ESI,† TS-4C and TS-4D). In this way, the insertion of SCO on thiirane **7** may take place, attacking on either of its strained carbons, by a S_N2-type sequence. This fact hinders the outcome of the whole transformations **1** (epoxide) → **4** (DTC) → **7** (thiirane) → **2** (TTC), particularly in those cases in which the intermediate thiirane **7** is unsymmetrically substituted, or possesses a stereogenic centre. Under this scenario, an even-number of downward attacks on the stereogenic carbon of **7** will always preserve the pristine stereochemical configuration. On the contrary, an odd-number of nucleophilic attacks or their combination with SCO/CS_2 reinsertions on the same carbon can result in the modification of the starting stereochemistry.

18 Similarly, at 100 °C, CS_2 could be reversibly extruded from TTC **2**, and reincorporated on thiirane **7**. The same stereochemical issues arise.