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Regio- and Stereoselective Synthesis of Dithiocarbonates under Ambient and Solvent-Free Conditions

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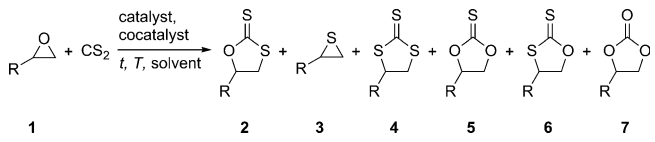
Herein, we report on the utilization of readily available lithium *tert*-butoxide as an efficient catalyst for the addition of carbon disulfide to terminal and internal epoxides under ambient conditions. Notably, the reaction proceeds regio- and stereoselectively. By applying the optimized conditions, 14 terminal and internal epoxides were converted. The desired cyclic dithiocarbonates were isolated in yields up to 95% after simple filtration over silica. NMR spectroscopy experiments to identify the mode of activation were performed, and they indicated activation of carbon disulfide by the catalyst. The reaction of *cis*-2,3-butyleneoxide gave only the *trans*-dithiocarbonate, whereas the conversion of (*R*)-propylen oxide gave the respective thiocarbonate stereoselectively as one enantiomer (>99% *ee*) in 87% yield.

In recent years, efforts have been intensified to utilize carbon dioxide as a C_1 building block, because it is regarded as readily available, inexpensive, and an abundant carbon source.[1] In this context, atom-efficient carbon dioxide fixation and valorization into cyclic carbonates is an elegant and frequently studied reaction.[2] Carbon disulfide is an isoelectronic analogue of carbon dioxide. It can be produced through the reaction of, for example, charcoal from plants and sulfur from power plant fuel gases, and thus, carbon disulfide can also be considered as a sustainable and inexpensive C_1 building block. In contrast to the coupling of carbon dioxide with epoxides **1**, the atom-economic reaction with carbon disulfide leads to complex reaction mixtures, especially at elevated temperatures owing to oxygen/sulfur scrambling (Scheme 1).[3] This phenomenon was observed in the pioneering works of this field by Endo, North, and co-workers.[3,4]



Scheme 1. Products obtained by the cycloaddition of epoxides with CS_2.

Notably, cyclic dithiocarbonates **2** have attracted much attention owing to their radioprotective activity[5] and utilization in polymer synthesis.[6] Despite the complexity of this reaction, there have been several excellent accounts on the development of catalytic systems for the conversion of epoxides **1** with carbon disulfide. This includes reports on catalysts based on Lewis and Brønsted bases,[7] alkali metal salts,[3] as well as transition-metal complexes.[4,8] Even though advances have been made, those catalysts often require cocatalysts, solvents, long reaction times, and/or elevated temperatures. The latter leads to unwanted byproducts, for example, trithio- or poly(thio)carbonates. Thus, the selective synthesis of cyclic dithiocarbonates **2** from epoxides **1** and carbon disulfide under mild and solvent-free conditions is still a challenging task. Recently, we reported on various efficient one- and two-component catalytic systems for the conversion of carbon dioxide with epoxides.[9] As an extension of this work, we were interested in the selective addition of carbon disulfide to epoxides **1** to yield dithiocarbonates **2**. Notably, the carbon center of CS_2 is more electrophilic than the carbon center of carbon dioxide and is, therefore, more reactive. Thus, the coupling of CS_2 with epoxides **1** might be conducted under comparatively milder reaction conditions. As a test reaction, we chose the addition of CS_2 to 1,2-butyleneoxide (**1a**), which was studied at room temperature with a reaction time of 5 h to identify suitable catalysts for this reaction (Table 1). Initially, we utilized catalysts that are known to facilitate the conversion of CO_2 with epoxides (Table 1, entries 1–3).[9c–e,g] These bifunctional onium salts proved to be very active in CO_2 coupling reactions at elevated temperatures.[9d,g] However, the application of tri-*n*-butyl-(2-hydroxyethyl)ammonium iodide and tri-*n*-butyl-(2-hydroxyethyl)phosphonium iodide at room temperature did not result in the formation of desired cyclic dithiocarbonate **2a** (Table 1, entry 1). Similar results were obtained with the two-component catalyst system consisting of triethanolamine and potassium iodide, which showed high activity in the coupling of CO_2 to epoxides (Table 1, entry 2).[9e] In the presence of tetra-*n*-butylphosphonium bromide and tetra-*n*-butylammonium bromide, again no conversion to desired product **2a** was observed (Table 1, entry 3). Given that the conversion of **1a** into cyclic dithioester **2a** was not possible in the presence of those catalysts under the test conditions, we envisioned CS_2 activation by applying potassium *tert*-butoxide, which subsequently enabled the conversion with **1a**.[10] Unfortunately, no conversion was observed in the presence of 5 mol% of the alkoxide (Table 1, entry 4). LiBr, which was reported by Endo et al. as a catalyst for this reaction, gave 21% conversion and desired product **2a** with 76% selectivity (Table 1, entry 5).[3] We conceived the dual activation of epoxide **1a** by LiBr and CS_2 by an

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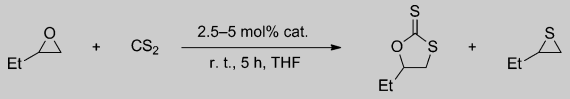
Table 1. Catalyst screening for the addition of CS_2 to **1a** as a test reaction.[a]



1a **2a** **3a**

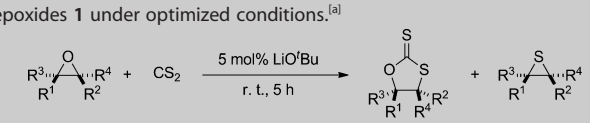
Entry	Catalyst	Conversion of **1a** [%][b]	Selectivity to **2a** [%][b]
1[c]	$[HO(CH_2)_2PBu_3]I$	11 (11)	0 (0)
2	$[HO(CH_2)_2]_3N$/KI	0	0
3[c]	$[Bu_4P]Br$	0 (4)	0 (0)
4	KO*t*Bu	3	0
5	LiBr	21	76
6	LiO*t*Bu, LiBr	>99	81
7	LiO*t*Bu	>99	78
8[d]	LiO*t*Bu	>99	88[e]
9[d,f]	LiO*t*Bu	>99	80[g]
10[d,h]	LiO*t*Bu	>99	90

[a] Reaction conditions: **1a** (2.5 mmol), catalyst (5 mol%), CS_2 (1.2 equiv.), THF (2.5 mL), RT, 5 h. [b] Conversions (of **1a**) and selectivity (to **2a**) were determined by GC with *n*-hexadecane as an internal standard. [c] For the conversion and selectivity in parentheses the respective ammonium salt was used. [d] Solvent-free. [e] Thiirane **3a** was observed as the only byproduct in 8% yield. [f] Catalyst (2.5 mol%). [g] Besides a 5% yield of **3a**, an oligomeric byproduct was obtained. [h] CS_2 (2 equiv.).

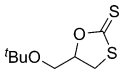
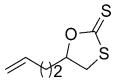
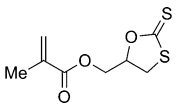
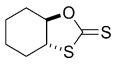
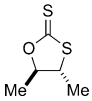
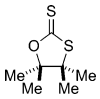
alkoxide. Thus, we combined LiBr and lithium *tert*-butoxide and observed a significant improvement in selectivity to 81% (Table 1, entry 6). Notably, similar results were obtained in the absence of LiBr (Table 1, entry 7). The selectivity was further improved by performing the reaction under solvent-free conditions by utilizing 5 mol% of lithium *tert*-butoxide (Table 1, entry 8). Thiocarbonate **2a** was obtained with 88% selectivity, whereas the only observed byproduct was thiirane **3a**. Even though full conversion was achieved in the presence of 2.5 mol% of lithium *tert*-butoxide, the formation of considerable amounts of an oligomeric byproduct was observed (Table 1, entry 9). Nevertheless, the best result was achieved by utilizing 5 mol% of lithium *tert*-butoxide as the catalyst and 2 equivalents of CS_2, which yielded 90% of desired product **2a** (Table 1, entry 10).

Subsequently, we evaluated the substrate scope for terminal and internal epoxides **1a–l** (Table 2). Under the optimized reaction conditions, desired products **2a–l** were isolated by simple filtration over silica gel. Terminal alkyl-substituted epoxides **1a–c** were efficiently converted with CS_2 into corresponding dithiocarbonates **2a–c** in high yields up to 92% (Table 2, entries 1–4). Full conversions of 1,2-epoxybutane (**1a**) and 1,2-epoxyhexene (**1b**) were achieved after 5 h and yields of 86% for **2a** and 92% for **2b** were obtained (Table 2, entries 1 and 2). In both cases, corresponding thiirane **3** was observed in 7% yield. The application of propylene oxide (**1c**) as the substrate yielded **2c** in only 16% yield after 5 h (Table 2, entry 3). However, prolonging the reaction time from 5 to 24 h resulted in full conversion of **1c**, and **2c** was isolated in 84% yield (Table 2, entry 4). In this case, byproduct **3c** was formed in only 1% yield. However, respective trithiocarbonate **4c**, which was presumably obtained by the conversion of **3c** with CS_2, was obtained in 5% yield. The reaction of benzyl-substituted oxirane **1d** with CS_2 showed high selectivity towards respective dithiocarbonate **2d**, which was isolated in 93% yield (Table 2, entry 5). Furthermore, *tert*-butyl glycidyl ether (**1e**) was converted with excellent selectivity into **2e** (Table 2, entry 6). In this case, the formation of thiirane **3e** was not observed. Moreover, unsaturated substrates **1f–h** were converted, and desired unsaturated cyclic dithiocarbonates **2f–h** were obtained in yields ≥89% (Table 2, entries 7–9). Glycidyl methacrylate derivative **2g** is of particular interest, because it might be an interesting monomer for novel polymers and materials

Table 2. Evaluation of the substrate scope for the coupling of CS_2 with epoxides **1** under optimized conditions.[a]



1 **2** **3**

Entry	Substrate	Product	Yield of **2** [%][b]	Yield of **3** [%][c]
1	**1a**		86	7
2	**1b**		92	7
3			16	–
4[d]	**1c**		84	1
5	**1d**		93	4
6	**1e**		92	–
7	**1f**		93	5
8	**1g**		89	–
9	**1h**		90	4
10	**1i**		95	1
11	**1j**		65	24
12[e]	**1k**		48 (23)	37 (65)
13			–	–
14[f]	**1l**		69	6

[a] Reaction conditions: **1** (2.5 mmol), LiO*t*Bu (5 mol%), CS_2 (2 equiv.), RT, 5 h. [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy. [d] $t = 24$ h, yield of trithiocarbonate: 5%. [e] *cis*-2,3-Butyleneoxide (*cis*-**1k**); the values in parentheses were obtained for the *trans* isomer (*trans*-**1k**). [f] $T = 90\,^\circ C$, $t = 24$ h.

(Table 2, entry 8).[11] Yet, sterically more demanding substrates **1h** and **1i**, that is, those disubstituted at the α-carbon atom, were converted to give **2h** in 90% yield and **2i** in 95% yield, respectively (Table 2, entries 9 and 10). Furthermore, we employed internal oxiranes **1j** and **1k** to gain insight into the mechanism and the stereochemistry of the reaction (Table 2, entries 11 and 12). Cyclohexene oxide (**1j**) was fully converted within 5 h to give cyclic xanthogenate **2j** in 65% yield and thiirane **3j** in 24% yield (Table 2, entry 11). Additionally, small amounts of oligomeric byproducts were observed. The configuration of product **2j** is, in accordance with literature and spectroscopic data of the isolated compound, identified as *trans*-**2j**.[3,8a] Upon employing *cis*-2,3-butylene oxide (*cis*-**1k**), desired product **2k** was isolated as the *trans* stereoisomer in 48% yield (Table 2, entry 12). Respective byproduct **3k** was obtained as the *cis* isomer in 37% yield. Notably, *trans*-**1k** gave *cis*-**2k** and *trans*-**3k** in yields of 23 and 65%, respectively. The inversion of the configuration of one of the two stereogenic carbon centers by applying *cis*-2,3-butylene oxide (*cis*-**1k**) indicates nucleophilic attack of an in situ formed xanthogenate at the oxirane. Finally, we studied the conversion of highly substituted substrate **1l**. By applying the standard reaction conditions, no conversion to the desired product was observed. However, at a higher temperature and with a longer reaction time (90 °C, 24 h), **2l** was isolated in 69% yield. After recrystallization of **2l**, crystals suitable for X-ray crystallographic analysis were obtained (Figure 1). Owing to strong ring strain, the newly fused heterocycle of **2l** differs clearly from planarity.

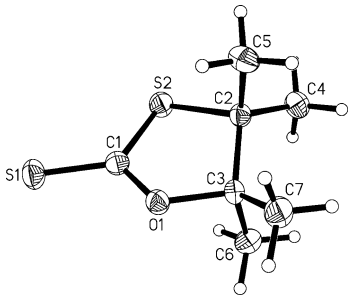


Figure 1. Molecular structure of **2l** in the crystal. Only one of the four molecules of the asymmetric unit is depicted. Displacement ellipsoids are drawn at the 30% probability level. (See the Supporting Information for crystallographic data).

The activation of CS_2 in this reaction by various nucleophiles, for example, amines,[8a] amidines,[12] and carbenes,[13] has been reported. Thus, we assume initial activation of CS_2 by nucleophilic attack of *tert*-butyl alkoxide and thus the in situ formation of xanthogenate **8** (see also Scheme 3). To obtain evidence for this hypothesis, we initially converted lithium *tert*-butoxide with equimolar amounts of CS_2 to yield **8**. Unfortunately, all attempts to isolate lithium xanthogenate **8** were not successful. Furthermore, we performed ^{13}C NMR spectroscopy experiments with equimolar mixtures of CS_2 and lithium *tert*-butoxide as well as non-nucleophilic $LiClO_4$ in [D_6]DMSO (Figure 2). Figure 2A shows the ^{13}C NMR spectrum of neat CS_2 with a characteristic chemical shift of the quaternary carbon atom at $\delta =$ 192.5 ppm. As expected, no shift occurred in the presence of the non-nucleophilic lithium salt $LiClO_4$ compared to pure CS_2 in [D_6]DMSO (Figure 2B). Those observations are in accordance with the literature.[3] Figure 2C depicts the ^{13}C NMR spectrum of neat LiO*t*Bu. The resonances at $\delta = 35.3$ and 65.9 ppm are assigned to the primary carbon atoms and the quaternary carbon atom of the *tert*-butyl group, respectively. A significant downfield shift in the ^{13}C NMR spectra for the resonances of CS_2 and the $-C(CH_3)$ moiety as well as an upfield shift for the resonances of the methyl groups $-C(CH_3)$ for a 1:1 mixture of LiO*t*Bu/CS_2 is observed. This distinctly indicates the in situ activation of CS_2 by the alkoxide.

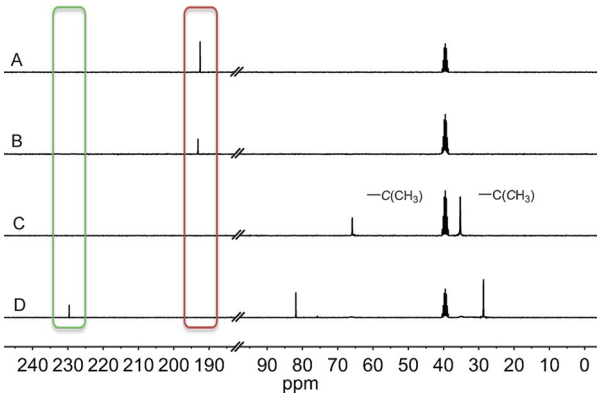
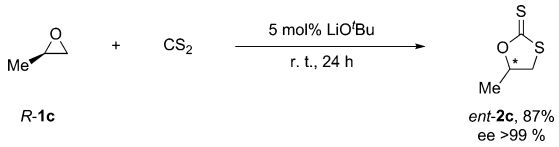


Figure 2. Sections of the ^{13}C NMR spectra in [D_6]DMSO: A) neat CS_2, B) $LiClO_4/CS_2$ (1:1), C) neat LiO*t*Bu, and D) LiO*t*Bu/CS_2 (1:1).

We postulate that the reaction proceeds through an S_N2 mechanism. Thereby, nucleophilic attack of in situ formed xanthogenate **8** occurs most probably at the sterically less hindered carbon atom of epoxide **1**. Consequently, the conversion of enantiomerically pure (*R*)-**1c** gave product *ent*-**2c** with >99% enantiomeric excess (*ee*) (Scheme 2). This suggests an S_N2 mechanism, as an S_N1 reaction at the higher substituted carbon atom would lead to partial racemization and, thus, to a lower enantiomeric excess value of the product.

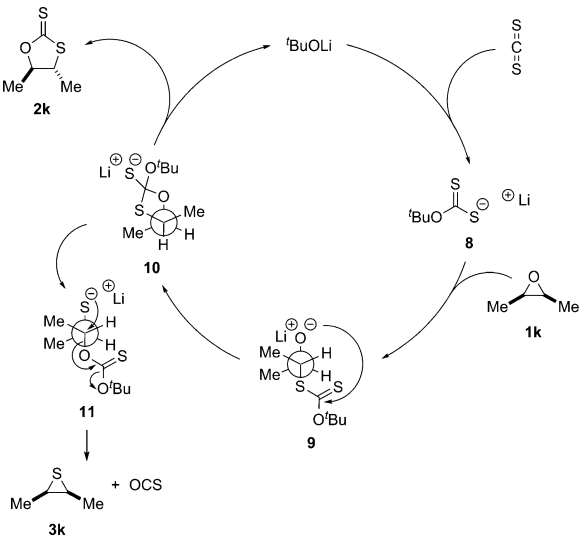


R-**1c**

ent-**2c**, 87% ee >99 %

Scheme 2. Stereo- and regioselective conversion of (*R*)-**1b** with CS_2.

On the basis of the conversion of *cis*-2,3-butyleneoxide (*cis*-**1k**), we propose the mechanism depicted in Scheme 3. The initial step is activation of CS_2 by LiO*t*Bu. Subsequent nucleophilic attack of formed xanthogenate **8** leads to **9**. This step might also be facilitated by additional Lewis acid activation of the oxirane by the lithium ion, similar to the activation by bimetallic aluminum(salen) complexes reported by North and co-workers.[8a] However, the attack occurs from the backside of the oxirane ring, and as a result, **9** is formed with the relative stereo-



Scheme 3. Postulated mechanism for the conversion of **1k** in the presence of Li*O*t*Bu* and CS_2 as an illustrative example.

chemistry illustrated by the Newman projection in Scheme 3. Rotation around the internal carbon–carbon σ bond and subsequent ring closure leads to **10**. Elimination of Li*O*t*Bu* regenerates the catalyst and gives rise to desired product **2k**. The proposed mechanism is in accordance with the observation that in the conversion of *cis*-2,3-butylene oxide (*cis*-**1k**) only *trans*-**2k** is formed. The stereoselective formation of *cis*-**3k** can be explained by ring opening of **10** to thiolate **11**. Rotation around the internal carbon–carbon σ bond gives rise to a conformation that permits an intramolecular S_N2 reaction to yield *cis*-**3k** and OCS, which has been detected by GC–MS. Thus, the double inversion in the overall process yields selectively only the *cis* isomer of **3k**.

In summary, we report on the utilization of lithium *tert*-butoxide as an efficient catalyst for the addition of carbon disulfide to terminal and internal epoxides under ambient and solvent-free conditions. Twelve epoxides were converted into the respective cyclic dithiocarbonates, and the desired products were obtained in yields up to 95%. NMR spectroscopy experiments revealed that carbon disulfide was activated by the alkoxide. On the basis of those spectroscopy investigations and the regio- and stereoselectivity of the reaction, a mechanism was proposed. Extension of the substrate scope, for example, to other substrate classes, is currently under investigation.

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