Computational, ReactIR-, and NMR-Spectroscopic Investigations on the Chiral Formyl Anion Equivalent *N*-(α-Lithiomethylthiomethyl)-4-isopropyl-5,5-diphenyloxazolidin-2-one and Related Compounds

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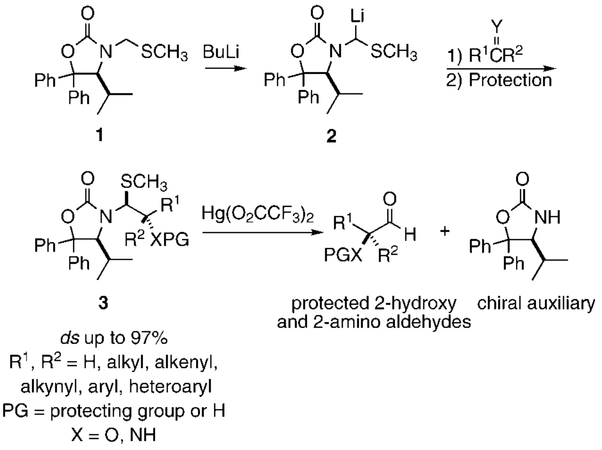
Dedicated to Professor Leopold Horner, in admiration, on the occasion of his 90th birthday

Abstract: The 4-isopropyl-3-methylthiomethyl-5,5-diphenyloxazolidin-2-one is readily lithiated in THF on the exocyclic CH_2 group ($\mathbf{1} \rightarrow \mathbf{2}$) to give a synthetically useful chiral nucleophilic formylating reagent. We have now studied the lithiation reaction by ReactIR spectroscopy and the structure of the organolithium reagent by computational methods and by NMR-spectroscopic measurements. The lithiation is complete at $-78\,^{\circ}C$ within 90 seconds, and it is accompanied by a decrease of the C=O wavenumber by 50 cm^{-1}. The NMR data (collected in $[D_8]THF$) give no evidence for $^{13}C,^{6}Li$ coupling or for aggregation; from DPFGSE-ROE spectra the single diastereoisomer of the lithium compound **2** seen in the NMR spectra (NMR-spectroscopic measurements from -105 to $-20\,^{\circ}C$) is assigned *like* configuration; the $^{13}C{=}O$ signal of the oxazolidinone undergoes a 7 ppm downfield shift upon lithiation ($\mathbf{1} \rightarrow \mathbf{2}$); line-shape analyses of the signals from the diastereotopic CH_2 and CMe_2 protons in lithiated 4,4-dimethyl-3-methylthiomethyloxazolidin-2-one (model compound **7**) reveal a $\Delta H^{\neq}$ of 8.9 ± 0.2 kcal$\,mol^{-1}$ for enantiomerization. The theoretical calculations provide an energy-minimum structure for the lithium compound **2** with coordination of the carbonyl oxygen to lithium, with an antiperiplanar arrangement of the C,Li and S,CH_3 bonds, and with relative *like* configuration of the two stereocenters—in perfect agreement with the conclusions from the IR- and NMR-spectroscopic measurements!

Keywords: chiral formyl anion equivalent · computational methods · IR spectroscopy · NMR spectroscopy · structure elucidation

Introduction

We have recently shown that the *N,S*-acetal derivative **1** can be directly lithiated (BuLi, THF, $-75\,^{\circ}C$) to the lithium compound **2** which is used as a nucleophilic formylating reagent. Reactions with aldehydes, unsymmetrical ketones, and imine derivatives are highly diastereoselective, producing adducts of type **3** which can be cleaved to aldehydes or derivatives thereof, with recovery of the chiral oxazolidinone auxiliary (Scheme 1).[1]



Scheme 1. Overall enantioselective formylation of carbonyl compounds by *N*-(α-lithiomethylthiomethyl)-4-isopropyl-5,5-diphenyloxazolidin-2-one (**2**).

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The lithium reagent **2** may be considered as having been formed by a heteroatom-directed metallation[2–6] of a CH_2 group which is additionally acidified by a SCH_3 substituent.[7–9] In order to better understand the stereochemical course of the reaction of compound **2** with electrophiles, it is necessary to obtain detailed information about its structure. There are a few crystal structures of organometallic compounds of the general formula **A** (Figure 1),[10, 11] and there are more structures of lithiated thioethers and thioacetals (formula **B**, Figure 1).[12–14] The typical structural features of **A** and **B** can be described as follows: In the metallated derivatives **A** there is always a five-membered ring chelate, with the metal atom coordinating to the carbonyl oxygen, as indicated in the formula. This coordination leads to a shift of the IR frequency of the C=O group to lower wavenumbers,[15, 16] whereas the C=O bond lengths hardly increase according to X-ray structures.[10, 11] In compounds of general type **B**, the C,Li bond is always in an antiperiplanar orientation to the S,C bond (in six-membered rings the lithium atom is always in an equatorial position). This conformation is stereoelectronically stabilized, resulting in a lengthening of the S,C bond and a shortening of the S,CLi bond.

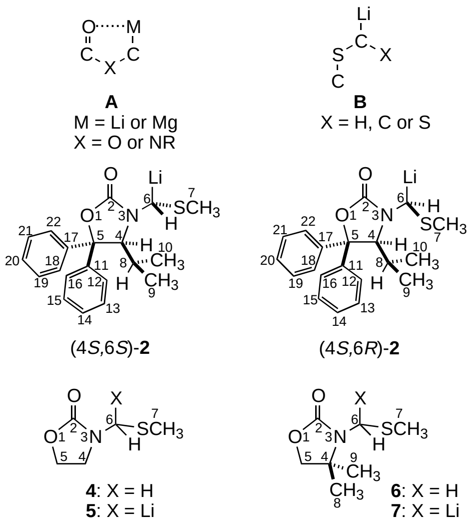


Figure 1. Formulae and numbering of atoms in compounds discussed in this paper.

The lithium reagent **2** can be described as a combination of **A** and **B**. Hence, both, the structural characteristics of **A** and **B**, should be present in compound **2**. In the present paper, our studies on the structure of **2** by a combined approach, including computational methods, as well as IR-, and NMR-spectroscopic measurements, are described.

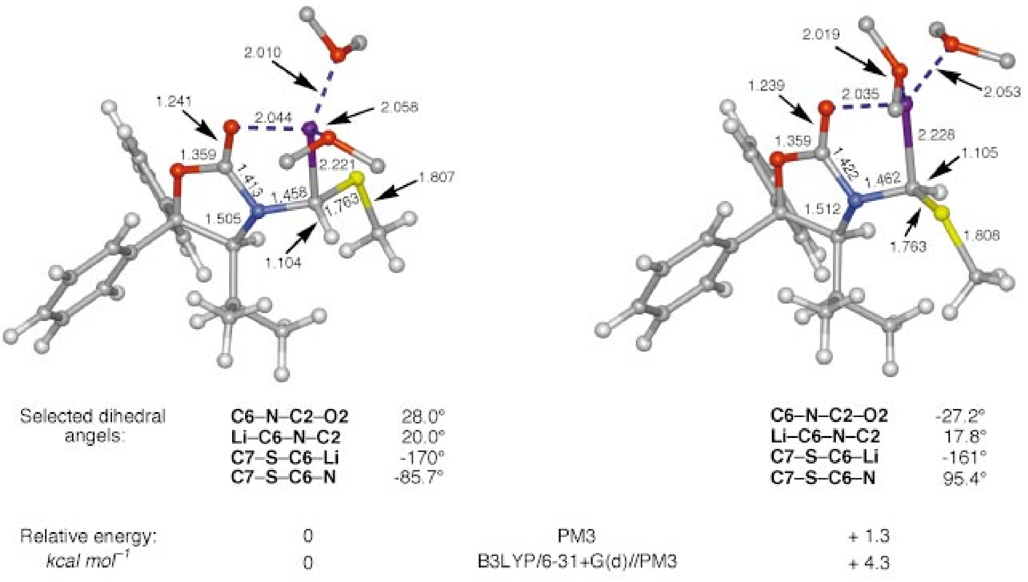
Results and Discussion

Computational studies: First, a computational investigation was undertaken to gain insight into the structure and stability of the two diastereoisomeric lithiated oxazolidinones (4*S*,6*S*)-**2** and (4*S*,6*R*)-**2** (Figure 1). We wanted to keep the system as authentic as possible to accurately account for all bonded and non-bonded interactions in the system. To be able to do this with a reasonable amount of computational resources we chose a combined semiempirical and density functional approach. The semiempirical PM3 method[17] with Anders' lithium parameters[18] has been widely used in organolithium chemistry.[19] The PM3 calculations have been shown to adequately reproduce geometries of organolithium compounds from experiments and higher level ab initio and density functional theory (DFT) methods.[20] However, the energies obtained by the PM3 method are usually not as exact.[21] Recently, Abbotto et al. have demonstrated that energies obtained by using density functional theory with the B3LYP hybrid functional with standard basis sets (6-31+G(d), 6-311+G(d)) on the PM3-optimized geometries (B3LYP/6-31+G(d)//PM3) reproduce high level results (B3LYP/6-31+G(d)//B3LYP/6-31+G(d)) with high accuracy.[22] Thus, we decided to apply this B3LYP//PM3 method for our calculations.

Initially, we performed a complete conformer search (Monte-Carlo) for the two diastereoisomers (4*S*,6*S*)-**2** and (4*S*,6*R*)-**2** in the absence of solvent molecules using the PM3 method. The energies of the two lowest energy conformers resulting from this search were then calculated at the B3LYP/6-31+G(d) level of theory. Two dimethyl ether ligands, commonly used as coordinating solvent molecules in computational studies, were added to each of the lowest energy conformations and a geometry optimization (PM3) was performed.[23] Several initial arrangements of the solvent molecules were tested to assure that the global minimum was found. Again, the resulting structures were subjected to single-point energy B3LYP/6-31+G(d) calculations. The result of these calculations is shown in Figure 2.

The (4*S*,6*S*)-diastereoisomer is energetically clearly preferred over the (4*S*,6*R*)-diastereoisomer. The difference in energy between the two stereoisomers amounts to 1.3 kcal mol^{-1} on the semiempirical level, while this value increases to 4.3 kcal mol^{-1} on the higher B3LYP/6-31+G(d)//PM3 level. The tendency of the DFT method to make a clearer distinction between the two diastereoisomers was also observed when calculating the single-point energies of the unsolvated molecules; the energy difference between the two isomers was then 6.1 kcal mol^{-1}. The significantly higher energy of (4*S*,6*R*)-**2** compared with (4*S*,6*S*)-**2** can be interpreted as a consequence of steric hindrance: The SCH_3 and the *i*Pr substituent in (4*S*,6*R*)-**2** are on the same side of the bicyclic system.

Apart from the restrictions imposed by the stereogenic centers, the structures of (4*S*,6*S*)-**2** and (4*S*,6*R*)-**2** are very similar. Both complexes display the usual distances and angles around the lithium atom which is coordinated by the carbonyl oxygen of the chiral auxiliary via a five-membered ring chelate. Such an internal chelation was calculated to account for a stabilization energy of 28 kcal mol^{-1} in a comparable system.[24] Although this value should be treated with caution (solvation of the lithium atom has not been included in the calculations), it indicates the high tendency for this type of intramolecular coordination. The carbonyl oxygen serves as a perfectly located coordination site, and therefore keeps the nitrogen and sulfur atoms from coordinating to lithium, as is



(4*S*,6*S*)-**2**

(4*S*,6*R*)-**2**

Figure 2. PM3-optimized geometries of the two diastereoisomers (4*S*,6*S*)-**2** and (4*S*,6*R*)-**2**. Key bond lengths, and dihedral angles are shown together with the relative energies as calculated at the B3LYP/6-31+G(d)//PM3 level of theory.

sometimes observed in α-heteroatom-stabilized organolithiums without additional intramolecular coordination sites. Furthermore, in both calculated structures, (4*S*,6*S*)-**2** and (4*S*,6*R*)-**2**, the methine proton H8 is pointing into the "*cis*"-phenyl group on the oxazolidinone ring, thereby directing the two methyl groups of the *i*Pr substituent towards the reaction center at C6. Thus, the "*cis*"-phenyl group forces the *i*Pr group into a conformation in which it mimicks a *t*Bu group. As proposed earlier,[25, 26] this effect can lead to superior levels of diastereoselectivity. Another interesting structural feature may be seen in Figure 2: the S,CH_3 bond is always in an antiperiplanar orientation (*anti* conformation) with respect to the C,Li bond, even when this is associated with severe steric repulsion as in the case of (4*S*,6*R*)-**2**. All attempts to turn the SCH_3 group out of this plane, that is to reduce the steric interaction with the *i*Pr group by rotation around the C7-S-C6-Li dihedral angle, resulted in re-optimization of the structure to the *anti* conformation. Therefore, we decided to further investigate this strong preference for the *anti* conformation, obviously caused by stereoelectronic effects (sometimes also called negative hyperconjugation).

Three mechanisms have been proposed to account for the stability of sulfur stabilized carbanions, namely polarization, d-orbital participation, and hyperconjugation. According to current understanding, hyperconjugation plays the largest role in determining α-heteroatom stabilization.[27–31] This mechanism involves double bond/no bond resonance structures such as:

$$H_3C{-}S{-}CH_2^{\ominus} \leftrightarrow H_3C^{\ominus} \quad S{=}CH_2$$

In an equivalent MO model this stabilization is interpreted as donation of electron density from the carbanionic center to the adjacent σ^*_{C-S} orbital.

To investigate the energy dependence on the C7-S-C6-Li dihedral angle, model compound **5** was chosen. To the best of our knowledge, only two studies concerning the energy dependence on rotation around a S,$C^{\ominus}$ bond have been carried out.[30, 32] Both of these studies did not include $Li^{\oplus}$ as a counterion. Full geometry optimization of **5** at the B3LYP/6-31+G(d) level of theory resulted in the structure shown in Figure 3 (right-hand side). The calculated structure bears close resemblance to the original system in Figure 2. This demonstrates, once more, the efficiency of the semiempirical PM3 method for obtaining reasonable geometries of organolithium compounds. Rotation around the C7-S-C6-Li dihedral angle in steps of 10°, followed by restricted geometry optimization (again at the B3LYP/6-31+G(d) level), produced the graph shown in Figure 3 (left-hand side). The same calculation in the absence of the lithium atom resulted in higher barriers of rotation by about 5 kcal mol^{-1} (see Supporting Information for the corresponding graph).

As expected, the *anti* conformation does indeed have the lowest energy. The main reason for this appears to be efficient stereoelectronic stabilization. As can be seen in Table 1, this conformation has the shortest C6–S bond length and the longest S–C7 bond length, the consequence expected for $n_C \rightarrow \sigma^*_{C-S}$ donation. The conformation in which the S,CH_3 bond is in a synperiplanar orientation (*syn* conformation) with respect to the C,Li bond is only slightly higher in energy. This indicates that stabilization through overlap of the n_C orbital with the σ^*_{C-S} orbital is also present in the *syn* conformation (here, the C6–S bond length is only slightly longer and the S–C7 distance only slightly shorter than in the *anti* conformation).

Upon anticlockwise rotation from the conformer with the synperiplanar orientation a local maximum is first reached at about −65°, corresponding to a *gauche* conformation. A local minimum is passed at about −90°, another local maximum is

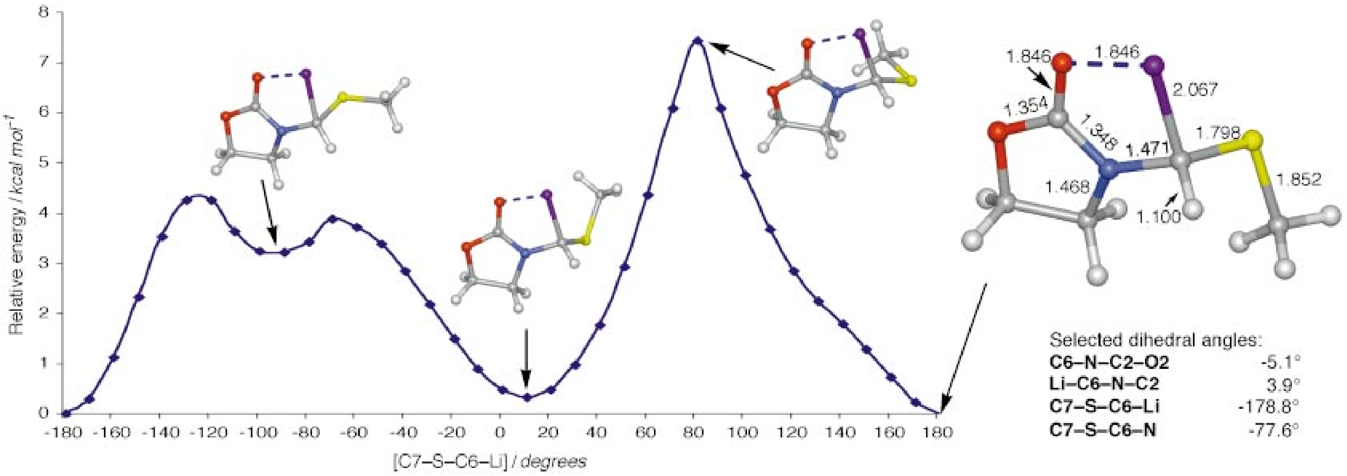


Figure 3. Left: Potential energy of **5** as a function of the C7-S-C6-Li dihedral angle. Structural parameters for the conformations displayed are summarized in Table 1. Right: B3LYP/6-31+G(d) optimized geometry of model compound **5**.

Table 1. Selected structural parameters of **4** and of conformations of **5** as highlighted in Figure 3. Numbering is according to Figure 1. Bond lengths are in Å and angles in degrees. Bond lengths discussed in the accompanying paragraphs are marked **bold**.

Structural parameter [Å] or [°]	Non-lithiated **4**	Conformation of **5** C7-S-C6-Li dihedral angle [°] −89	18	91	179
O2–Li	–	1.884	1.834	1.890	1.846
C2–O2	**1.210**	**1.239**	**1.247**	**1.240**	**1.245**
C2–N	**1.382**	**1.355**	**1.344**	**1.353**	**1.348**
N–C6	1.435	1.449	1.472	1.442	1.471
C6–H6	1.099	1.093	1.096	1.090	1.100
C6–Li	–	2.012	2.070	2.019	2.067
C6–S	**1.854**	**1.921**	**1.831**	**1.944**	**1.798**
S–C7	**1.827**	**1.827**	**1.834**	**1.838**	**1.852**
Li–S	–	**2.582**	**3.298**	**2.463**	**3.124**
S-C6-Li	–	80.0	115.3	76.8	107.7

reached at about −120°. The conformation at about −90°, with the S,CH_3 bond perpendicular to the C,Li bond, is characterized by a close Li–S distance (2.58 Å), which may indicate coordination of sulfur to lithium (Table 1; a mean Li–S bond length of 2.563 Å is retrieved from the Cambridge Structural Database (CSD)[33]). This stabilizing interaction is also present in the corresponding structure at +90°, although no minimum is observed in this case, since this point coincides with the point having the most unfavorable contact between the SCH_3 group and the five-membered ring. This stabilizing Li,S interaction (as in the conformations at −90° and +90°) would probably not have been observed, if solvent molecules had been included in the calculations. One solvating molecule would then have to give up the coordination to lithium, in order to allow the sulfur atom to coordinate to lithium (see the Supporting Information for a PM3 study in the presence of solvating molecules). Including solvating dimethyl ether ligands in some key structures of Figure 3, and then performing single-point energy B3LYP/6-31+G(d)//PM3 calculations, resulted in an increased energy of the structure having the C7-S-C6-Li dihedral angle at 0° by 2.4 kcal mol^{-1} (relative to the 180° structure), while the structure having the C7-S-C6-Li dihedral angle at 270° is still about 7.5 kcal mol^{-1} higher in energy than the global minimum. Hence, the energy associated with rotation around the S,CLi bond is expected to be around 8 kcal mol^{-1} in solution.

It is interesting to note that a lengthening of the C=O bond (and a shortening of the C2,N bond) is observed for the lithiated compound **5** compared with **4** (Table 1). This bond lengthening is caused by internal coordination of the carbonyl oxygen to lithium (a main characteristic of all 36 calculated conformers of **5**, as well as of (4*S*,6*S*)-**2** and (4*S*,6*R*)-**2**), and it has previously been concluded from IR-spectroscopic studies (see below),[15, 16] while it was present to a lesser extend in X-ray crystal structures.[10, 11]

It can be concluded from the model studies that rotation of the SCH_3 group in (4*S*,6*R*)-**2** (Figure 2) away from the *anti* orientation to reduce van der Waals interactions between the SCH_3 and the *i*Pr group does not compensate for the loss of stabilization by hyperconjugation.

IR-Spectroscopic studies: As mentioned, a key feature of all calculated conformers of compounds (4*S*,6*S*)-**2**, (4*S*,6*R*)-**2**, and **5** is the intramolecular coordination of the carbonyl oxygen to lithium, thereby defining a five-membered ring chelate. We decided to use ReactIR spectroscopy to obtain data regarding this coordination. The progress of the reaction of methylthiomethyl oxazolidinone **1** with BuLi in THF at −78 °C was monitored under inert atmosphere by IR spectroscopy. The IR spectrum of the starting material **1** displays a characteristic resonance at 1760 cm^{-1}, corresponding to the stretching frequency of the carbonyl group in **1** (Figure 4). When 0.33 equiv BuLi were added, a reduced intensity of the carbonyl band at 1760 cm^{-1} was observed, while a new absorption at 1710 cm^{-1} emerged which is assigned to the lithiated product **2**. Addition of another 0.66 equiv BuLi (2 × 0.33 equiv) resulted in complete disappearance of the band at 1760 cm^{-1}. The stretching frequency of the carbonyl group in **2** is shifted by 50 cm^{-1} to lower wavenumbers, as compared to **1**, which indicates a weakening of the C=O bond, obviously caused by intramolecular coordination of the carbonyl oxygen to lithium. Carbonyl stretch frequency shifts of 35 cm^{-1} to 60 cm^{-1} to lower wavenumbers upon complexation with

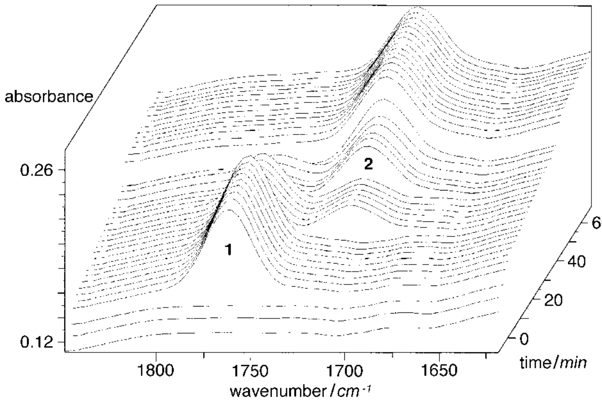


Figure 4. Metallation of methylthiomethyl oxazolidinone **1** to the corresponding lithiated species **2** by addition in portions of 1 equiv BuLi, monitored by ReactIR.

lithium have been reported before for similar systems.[15, 16] An inter- instead of an intramolecular Li,O coordination is highly unlikely, since such a coordination would be entropically disfavored.

The reaction profile of the experiment described above can be followed by plotting the intensities of the carbonyl absorbance at 1710 cm^{-1} and 1760 cm^{-1} against time (Figure 5). The data points displayed in Figure 5 are the average of 256 scans collected over approximately 90 s. As can be seen from the reaction profile, lithiation of methylthiomethyl oxazolidinone **1** by BuLi is very rapid: The lithiation (**1** → **2**) takes only 90 s at −78 °C in THF! This information is valuable for future preparations of **2** and similar compounds.

NMR-Spectroscopic studies: Orientational NMR experiments have shown that the lithiated methylthiomethyl oxazolidinone **2** is thermally stable at −50 °C over a period of several days. At temperatures above −20 °C, slow decomposition to the chiral auxiliary (Scheme 1) and several unidentified products is observed. No attempts have been made to analyze the resulting complex mixture.

The aggregation state of organolithium compounds may be conveniently deduced from the multiplicities due to scalar carbon–lithium coupling in the ^{13}C NMR spectra.[34] Lithium-6 is the preferred isotope in these experiments because it has a small quadrupole moment.[35] For our experiments aimed at the determination of the aggregation state of **2**, we employed Bu^{6}Li (96 % enrichment) for the lithiation of compound **1**. In two separate runs, **1** was treated with 0.5 equiv and with 2 equiv of Bu^{6}Li at −78 °C. The two resulting spectra of **2** were identical (apart from additional signals from excess **1** or from excess BuLi), indicating that no mixed aggregates between **2** and excess BuLi are formed. This conclusion is confirmed by the NOE measurements described below.

The ^{13}C signal of the lithiated carbon C6 does not reveal line splitting due to ^{6}Li coupling at −50 °C. At lower temperatures (down to −105 °C), the ^{13}C signal of C6 broadens considerably (more than those of the other signals), however, without revealing a multiplicity. Thus, the aggregation state of lithium compound **2** in THF is uncertain, but from the absence of mixed aggregates with excess BuLi we tentatively conclude that **2** is monomeric in THF.[36] This is confirmed by the independence of the ^{1}H and ^{13}C NMR spectra of **2** on the concentration and on the presence or absence of excess BuLi.

At all temperatures between −105 and −20 °C a single set of signals is observed in the ^{1}H and ^{13}C NMR spectrum of **2**. Thus, there is no indication for the co-existence of comparable amounts of the two diastereoisomers (4*S*,6*S*)-**2** and (4*S*,6*R*)-**2**. Hence, either the epimerization process is fast on the NMR timescale even at −105 °C, or the equilibrium lies completely on the side of one epimer.

In order to evaluate the dynamics of epimerization (configurational stability) at C6, we have carried out a series of temperature-dependent ^{1}H NMR measurements with the closely related compound **7**. Therein, the protons H8 and H9 on the geminal methyl groups (C8/C9) and the protons H5 on C5 are diastereotopic at −105 °C ($\Delta\nu = 13$ Hz and 108 Hz, respectively), thus, the lithiated carbon C6 is interconverting very slowly (if at all!) on the NMR timescale at this temperature. The temperature dependence of the H5 signals, together with a complete line-shape analysis of these signals is shown in Figure 6. The ^{1}H NMR line shapes were simulated using the program gNMR.[37] From an Eyring plot the activation parameters for the enantiomerization of **7** in THF were estimated to be

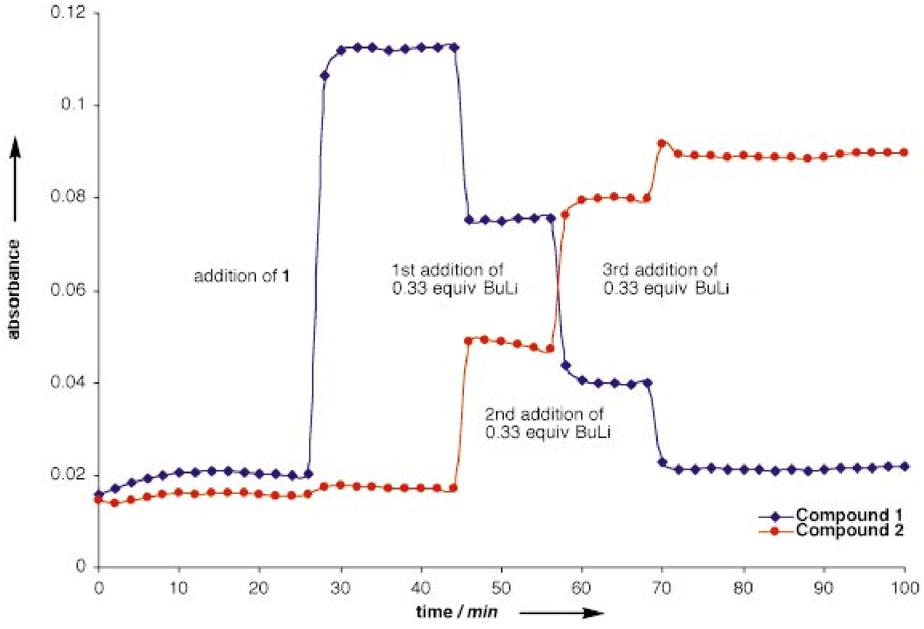


Figure 5. Reaction profile of the metallation of methylthiomethyl oxazolidinone **1** to the corresponding lithiated species **2** by addition in portions of 1 equiv BuLi.

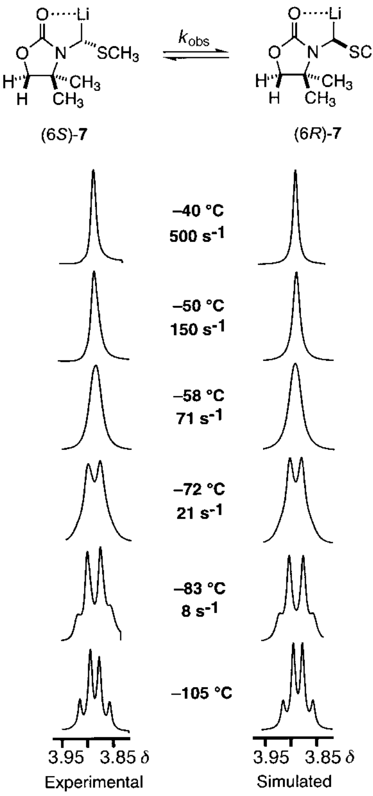


Figure 6. ^{1}H NMR line-shape analysis: Experimental (left) and calculated (right) variable temperature ^{1}H NMR signals of H5 of compound **7** in [D$_8$]THF.

$\Delta H^{\neq} = 8.9 \pm 0.2$ kcal mol^{-1} and $\Delta S^{\neq} = -8.9 \pm 4.2$ cal mol^{-1} K^{-1} ($\Delta G^{\neq}_{213\,K} = 10.8$ kcal mol^{-1}).[38] An analogous line-shape analysis for the signals of H8/H9 of the lithium compound **7** was complicated by the presence of a peak from butane (formed in the reaction of **6** with BuLi), but gave similar activation parameter values ($\Delta H^{\neq} = 9.3 \pm 0.3$ kcal mol^{-1}, $\Delta S^{\neq} = -7.2 \pm 4.0$ cal mol^{-1} K^{-1}, $\Delta G^{\neq}_{233\,K} = 11.0$ kcal mol^{-1}).[39]

The results obtained with **7** can be taken as evidence that C6 epimerization in **2** must also be slow on the NMR timescale at low temperatures. Hence, from the presence of only one set of signals even at −105 °C we conclude that we observe a single epimer of **2** in THF in the temperature interval −105 to −20 °C. Thus, at all temperatures the equilibrium between (4*S*,6*S*)-**2** and (4*S*,6*R*)-**2** must lie (nearly) completely on the side of the (4*S*,6*S*)-epimer.

It is noteworthy, that the lithiated *N*,*S*-acetal **7** decomposes at temperatures above −20 °C at a much faster rate than lithium compound **2**. This is probably due to the different substitution patterns of the two oxazolidinone derivatives: The C=O group of **2** is sterically protected by the geminal phenyl groups, whereas the C=O group of **7** is susceptible to nucleophilic attack.

In order to assign the configuration at C6, NOE measurements appeared to be the method of choice. In the case of one-dimensional NOE spectra (which are superior to two-dimensional methods with respect to sensitivity, resolution, and time requirement for small molecules), a major improvement has been introduced in recent years by the DPFGSE-NOE method (DPFGSE: double pulsed field gradient spin echo).[40] By using this pulse sequence the well-known disadvantages of the conventional difference NOE (subtraction artifacts) may be largely suppressed. However, the conventional steady-state difference NOE method as well as the DPFGSE-NOE method failed to yield interpretable results. Independent of the irradiation position, all NOEs were negative, and all ^{1}H signals were enhanced. This is typical for situations in the "slow-tumbling" regime with $\omega\tau > 1.12$ (ω = Larmor frequency, τ = correlation time).[41] Under these conditions the NOE is negative (same sign of irradiated and enhanced signal). Due to efficient spin diffusion in the steady state difference NOE experiment, the NOE is propagated to all proton positions,[41] thus prohibiting stereochemical assignments.

The negative NOE regime may be circumvented by spin-lock methods.[41] The well-known ROESY experiment is frequently employed to obtain two-dimensional spectra. To bring together the advantages of one-dimensional NOE spectroscopy and the spin-lock method, one of our groups[42] has recently introduced the rotating frame variant, DPFGSE-ROE, which yields positive NOEs throughout, regardless of the molecular size and the correlation time. Figure 7 shows a set of selected DPFGSE-ROE spectra of **2** at −50 °C. Irradiation with the frequency of H4 (Figure 7b) leads to

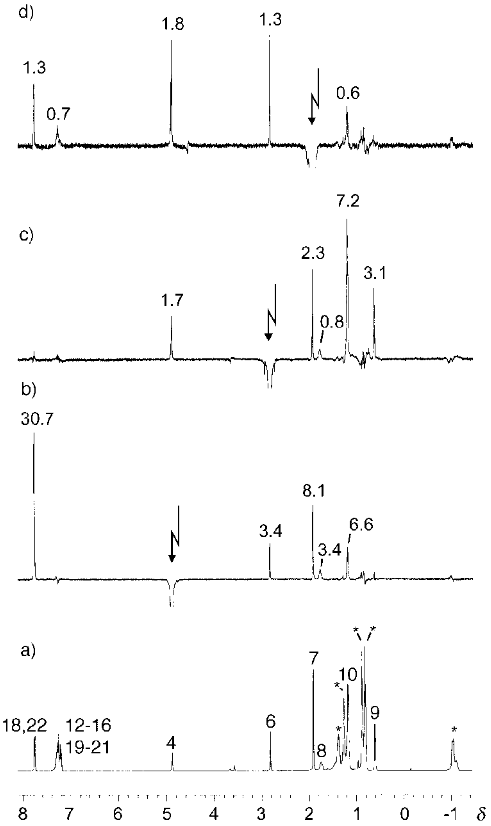


Figure 7. DPFGSE-ROE spectra of lithiated methylthiomethyl oxazolidinone **2** in the presence of 1 equiv BuLi, 500 MHz, [D$_8$]THF, −50 °C, spin-lock time 300 ms. a) regular ^{1}H NMR spectrum; b) irradiation with the frequency of H4; c) irradiation with the frequency of H6; d) irradiation with the frequency of H7. Numbers in a) are assignments and refer to Figure 1. Asterisks denote signals of BuLi and butane. Numbers in spectra b)–d) are percentage signal enhancements, as compared to the irradiated signal intensity = −100 %. No scaling of the percentage numbers to the numbers of involved protons has been made.

strong enhancement of the signals from the protons in the *ortho* position of the phenyl groups (H18/H22), as well as to moderate enhancement of the signals from H6 and H7, compatible with the structure of diasteroisomer (4*S*,6*S*)-**2** shown in Figure 2. Further evidence that the stereocenter at C6 has (*S*)-configuration, as suggested by the computational studies, comes from irradiation with the frequency of H6 (Figure 7c): Apart from the expected enhancements of the signals from H4 and H7, comparable strong enhancements (7.2% and 3.1%, respectively) of the *i*Pr group signals (H10 and H9, respectively) are observed. From the computed structures, a strong NOE only to H10 would be expected, if (4*S*,6*R*)-**2** would be present.

If the SCH_3 group would be directed towards the *i*Pr groups (as in (4*S*,6*R*)-**2**), irradiation at H7 should result in strong enhancement of the H9 and H10 signals. As can be seen in Figure 7d, irradiation with the frequency of H7 generates only weak NOEs on the signals of neighboring protons. It is surprising that even the enhancement of the H10 signal is fairly small, since a somewhat stronger NOE would be expected, if (4*S*,6*S*)-**2** really adopted the calculated conformation depicted in Figure 2. A possible explanation for a weak NOE between H7 and H10 is that the C,Li bond and the S,CH_3 bond are in an antiperiplanar orientation, but that the C,Li bond and the C=O bond are not parallel to each other (as suggested by the computer calculations), but rather slightly rotated away from each other (without breaking the Li,O coordination), thereby moving the SCH_3 group further away from the *i*Pr group (Figure 8).

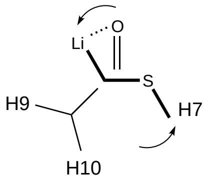


Figure 8. Schematic drawing of the conformation of compound (4*S*,6*S*)-**2** as discussed in the accompanying paragraph.

Based on the NMR-spectroscopic investigations we conclude that (4*S*,6*S*)-**2** is the sole diastereoisomer in THF at temperatures between −105 and −20 °C. This is in accordance with the theoretical studies.

Enhancement of the signals from excess BuLi was not observed in any of the DPFGSE-ROE experiments (irradiation with various frequencies belonging to **2**). This, again, strongly indicates that mixed **2**/BuLi aggregates are not formed in THF. Even small amounts of such aggregates should result in observable NOEs.

It is noteworthy, that the resonance of the carbonyl carbon of **2** ($\delta = 163.5$) is shifted downfield by about 7 ppm with respect to the corresponding carbon signal of **1** ($\delta = 156.8$) at −105 °C in [D_8]THF. This observation further substantiates the existence of an intramolecular coordination of the carbonyl oxygen to lithium in compound **2**, as concluded from the computational and ReactIR-spectroscopic studies.

Conclusion

A combination of three techniques, computational methods, IR and NMR spectroscopy, was used to investigate the structure of lithium reagent **2**. As suggested by our computational studies, and then confirmed by NOE measurements on **2** and coalescence experiments on model compound **7**, the stereocenter of the lithiated carbon C6 of the only diastereoisomer that is detected by NMR methods in the tested temperature range (−105 to −20 °C) has (*S*)-configuration. The strong preference of the (*S*)-configuration over the (*R*)-configuration in lithium compound **2** can be explained as follows: The five-membered ring chelate, with the carbonyl oxygen coordinating to lithium (as evident from all three methods of investigation), locks the Li-C6-N-C2 dihedral angle at about 20°. In the epimer with (*R*)-configuration at C6 the SCH_3 group would be forced into the *i*Pr group. Rotation of the SCH_3 group away from the *i*Pr group to release steric repulsion does not compensate for the loss of stereoelectronic stabilization. The importance of this $n_C \rightarrow \sigma^*_{C-S}$ delocalization was demonstrated with model compound **5**.

From the assignment of configuration at the lithiated carbon of **2** and the known product configuration in **3** we can conclude that Li/C replacement occurs with retention.

Experimental Section

General information (for the preparation of compounds **1** and **6**): All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in heat-gun dried glassware under an argon atmosphere. Tetrahydrofuran (THF) was freshly distilled from potassium under argon. Dichloromethane (CH_2Cl_2) and dimethyl sulfoxide (DMSO) were distilled from calcium hydride (CaH_2) and stored under argon over activated 4 Å molecular sieves. Triethylamine (Et_3N) was distilled from CaH_2 and stored under argon over KOH pellets. All other reagents and solvents were used as received from Aldrich or Fluka. Flash column chromatography (FC) was performed using Fluka silica gel (40–63 μm).

^1H NMR and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer (300 MHz); δ in ppm downfield of TMS ($\delta = 0$). IR spectra were measured on a Perkin–Elmer FT-IR 1600 spectrometer; (s = strong, m = medium, w = weak). High resolution mass spectra were recorded on a Ion Spec Ultima 4.7 FT Ion cyclotron resonance (ICR) mass spectrometer.

(*S*)-4-Isopropyl-3-methylsulfanylmethyl-5,5-diphenyloxazolidin-2-one (1): This compound and compounds **3** were prepared according to procedures previously described.[1]

4,4-Dimethyl-3-methylsulfanylmethyloxazolidin-2-one (6): Et_3N (24.0 mL, 172 mmol) and $ClCO_2Et$ (14.9 mL, 157 mmol) were added at −15 °C to a solution of 2-amino-2-methyl-1-propanol (15.0 mL, 157 mmol) in CH_2Cl_2 (450 mL). After stirring for 12 h at room temperature, the reaction mixture was quenched with 1M HCl solution and diluted with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was dissolved in 5%-methanolic NaOH and heated to reflux for 7 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, MeOH was removed under reduced pressure, and the residual mixture was diluted with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by trituration (pentane) afforded 4,4-dimethyloxazolidin-2-one[43] (10.7 g, 59%) as a colorless solid.

BuLi (21.0 mL, 32.6 mmol) was added at 0 °C to a solution of 4,4-dimethyloxazolidin-2-one (3.41 g, 29.6 mmol) in THF (25 mL). After stirring for 10 min, DMSO (125 mL) and chloromethyl methyl sulfide (MTMCl) (2.98 mL, 35.5 mmol) were added consecutively to the reaction mixture. After stirring for 4 h at rt, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and diluted with Et_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 ×). The combined organic layers were washed with H_2O (1 ×), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (1:1 pentane/Et_2O) afforded compound **6**

(1.70 g, 33%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 4.37$ (s, 2H; CH_2S), 3.99 (s, 2H; CH_2O), 2.23 (s, 3H; SMe), 1.40 (s, 6H; Me); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.67$, 75.30, 58.35, 44.40, 25.25, 15.10; IR ($CHCl_3$): $\tilde{\nu} = 2975$ (w), 2927 (w), 1742 (s), 1479 (w), 1418 (m), 1400 (m), 1384 (m), 1277 (m), 1178 (w), 1074 (m), 1032 (m) cm^{-1}; Hi-Res-MALDI: m/z (%): 396.1819 (21) $[2M{+}Na]^+$, 225.1573 (93) $[M{+}K]^+$, 198.0558 (100) $[M + Na]^+$ (calcd 198.0565), 137.0237 (91).

Computational methods: PM3-geometry optimizations, with parameters for lithium, were done on a dual processors Silicon Graphics Octane workstation with the Spartan 5.0 program package.[44] The parent structure was subjected to a complete conformer search and several initial geometries for the solvating ligands were optimized in order to find the global minimum. The structures were optimized with the keyword HHon switched on to eliminate the overly positive HH attraction of the PM3 method.[45] The vibrational frequencies were also calculated to verify that all optimized structures were minima on the potential energy surface. Single point energies, calculated using density functional theory (DFT) employing the B3LYP hybrid functional[46] with the SCF tight keyword on the PM3-optimized structures, were done on a Hewlett-Packard V2500SCA computer using the Gaussian 98 program package.[47] The standard valence double-z basis set 6-31+G(d) was used as implemented in the program. The conformational mapping of the C7-S-C6-Li dihedral angle in the model compound **5** was done in 10° steps, followed by restricted optimization at the B3LYP/6-31+G(d) level using the OPT = ModRedundant keyword in G98.

ReactIR Spectroscopy: The ReactIR experiments were conducted with an ASI Applied Systems ReactIR 1000 spectrometer with a MCT detector (MCT = mercury cadmium telluride) and a DiComp probe. The data points displayed are the average of 256 scans collected over approximately 90 s. The background spectrum was recorded in neat THF (3 mL) at −78 °C. A solution of compound **1** (230 mg, 0.674 mmol) in THF (2 mL) was added. BuLi (1.6 M in hexane) was added portionwise (3×0.17 mL) to the resulting mixture.

NMR Spectroscopy: NMR spectra were recorded on a JEOL Alpha 500 spectrometer (500 MHz) or on a Bruker AMX-400 (400 MHz). ^1H chemical shifts are referenced to the residual solvent signal of $[D_8]$THF at $\delta = 3.58$. All spectra were recorded after 30 min temperature equlibration; the reported temperatures were calibrated by an internal standard.[48] The pulse sequence DPFGSE-ROE was applied as described.[42] Preparation of the samples: A weighted amount of reactant **1** or **6** was placed in an NMR tube which was fitted with a serum cap. The tube was evacuated, heated, and purged with argon. Then, compound **1** or **6** was dissolved in dry (Na/Pb alloy) $[D_8]$THF (0.2 mL). In a separate small flask, an appropriate amount of Bu^6Li[49] in hexane was concentrated under reduced pressure and the residual oil was dissolved in $[D_8]$THF (0.3 mL) under argon. This solution was transferred slowly via syringe to the solution of **1** or **6** in $[D_8]$THF at −78 °C. Alternatively, compound **1** or **6** was dissolved in $[D_8]$THF (0.5 mL) and an appropriate amount of Bu^6Li was added neat as a thick yellow oil.

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