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Disulfide-based metal-free α-sulfanylation of ketones†

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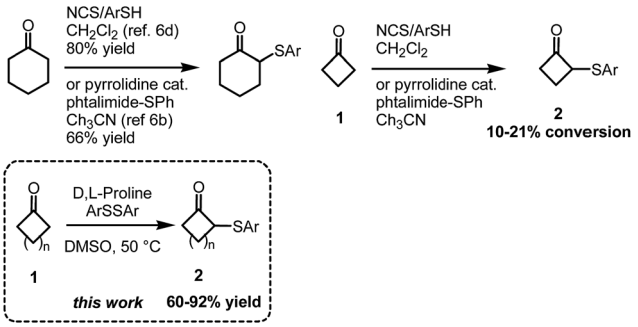
An eco-friendly methodology for the direct α-sulfanylation of ketones, has been developed. The procedure, based on the use of functionalized diaryldisulfides and catalyzed by D,L-proline, represents a mild and efficient approach for the preparation of α-arylthio-ketones.

Introduction

The development of new synthetic methodologies, able to access functionalized carbonyl compounds, is of great importance in contemporary organic synthesis. α-Sulfanylation of carbonyl compounds is particularly attractive because of the synthetic importance of these products as intermediates in many organic transformations and they are frequently used as crucial building blocks in the synthesis of drugs and bioactive compounds.[1] Among the most relevant strategies used for the introduction of a sulfanyl-unit, metal-catalyzed cross-coupling reactions[2] and organometallic-based transformations have been widely explored. Also it is very common to use strategies involving enolates[3] or enamine-transient species.[4] Again, nucleophilic α-halogen displacement reactions of halogenated ketones and aldehyde compounds[5] with thiolates have been frequently used as a principal way to access functionalized ketosulfides.

Nevertheless, all of these procedures, require multistep reactions in order to prepare the corresponding reactive enolates or by α-activation of the carbonyl compounds. Recently, new ketone sulfanylation reactions, based on the use of ArSCl, or NCS/ArSH reagents, have been reported as valid methods for the functionalization of a wide number of ketones.[6] Also, interesting results have been obtained by different research groups performing metal-free organocatalyzed procedures.[7] However, none of the methods can be considered widely versatile because of some limitation related to the commercial availability of the starting materials,[8] or in some cases, reaction conditions and yields are not easily scalable or limited to small scale reactions.[1] As a prosecution of our studies on the development of new metal-free synthetic strategies, involving the preparation and selective transformation of cyclobutane derivatives,[9] we paid attention to the synthesis of some α-phenylthio-substituted cyclobutanones[10] such as **2**, which has been used in many organic transformations.[5a,b] For this purpose, we valued several known α-sulfanylation methods.[5b,6b] However, no effective functionalization of cyclobutanone **1** was obtained when these conditions were adapted to this small carbocyclic ketone (Scheme 1). Moreover, along this screening, we observed that α-sulfanyl cyclobutanone **2a** might be easily prepared by the reaction of diphenyldisulfide with **1** in the presence of pyrrolidine-based catalysts and leading to the corresponding reaction products in excellent yields.



Scheme 1 α-Sulfanylation of cyclic ketones.

To our knowledge, there are just few examples of direct catalytic α-sulfanylation of unmodified carbonyl compounds which are based on the use of *N*-(phenylthio)phthalimide[6b] or sulfonyl chloride derivatives[6] but excluding the interesting results obtained by Enders and co-workers using tetramethylthiuram disulfide,[11] no examples of organocatalyzed reactions involving diaryldisulfides as reagents have been reported to date. In this paper we now wish to report the development of a new proline-catalyzed ketosulfide synthesis from aryldisulfides and ketones.

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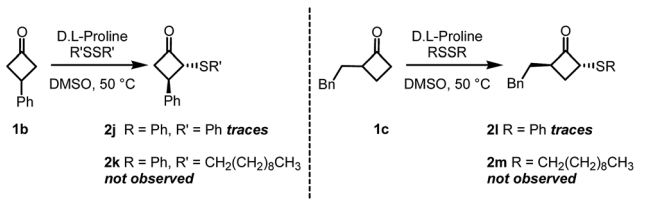
Results and discussion

We started this study by using diphenyldisulfide and cyclobutanone **1** in the presence of D,L-proline as catalyst in DMSO. The reactions, conducted at room temperature, afforded the corresponding ketosulfide **2a** in 18% yield after 16 hours. Further experiments, carried out at 50 °C gave better conversion and after chromatography, α-sulfanyl cyclobutanone **2a** was isolated in 90% yield. This result, encouraged us to pursue on this investigation by setting a series of reaction conditions including, reaction times, temperatures and solvents, keeping D,L-proline as catalyst. The results of this preliminary investigation are summarized in Table 1.

These experiments, confirmed DMSO as the solvent of choice for this transformation (entries 1–3). Moreover, the use of DMF resulted in lower yields (entries 4–5), while protic solvents such as MeOH were ineffective. Reduction of the temperature from 50 °C to room temperature or lower, drastically limited the reaction between the ketone and the disulfide compound (entries 1, 2 and 4). Encouraged by this result, we repeated the same reaction by using L-proline as catalyst in order to value a possible enantioselective version of this transformation. As expectable, analogous results in terms of yields and reaction times were achieved with those observed for D,L-proline but unluckily, HPLC analysis of the isolated cyclobutanone **2a** showed the formation of a racemate.[11] Reactions employing other chiral not racemic pyrrolidine-catalysts (see ESI†), were also inefficient in terms of asymmetric induction. We believe that this result can be rationalized by taking in consideration, the reduced formation of a stable hydrogen-bonding interaction between the disulfide and the transient enamine-adduct due to the operation high temperatures. However, this procedure is an easily applicable and effective synthetic procedure for the introduction of a phenylthio-functional group on a cyclobutanone. In order to better study this synthetic procedure and probe the scope of this ketone α-sulfanylation, cyclobutanone **1a** was functionalized by using a series of differently substituted diphenyldisulfides in the presence of D,L-proline as described in the Scheme 2.

All the diaryldisulfide derivatives reacted in good to excellent yields with cyclobutanone **1a**, affording the desired α-sulfanyl cyclobutanones **2b–g**. The reaction appear to be general without detectable differences using diaryldisulfides bearing EWG or EDG substituents on the aromatic ring. Moreover attempts to repeat this reaction by using dibenzyldisulfide or bis(*o*-carboxymethylphenyl)disulfide did not allowed us to observe the formation of appreciable amounts of the corresponding cyclobutanones **2h** and **2i**, even after 48 h.

As the unsubstituted cyclobutanones **2a–g** were easily prepared with the developed methodology, we valued the possibility to functionalize other cyclobutanone derivatives,



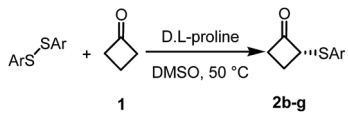
Scheme 2 α-Sulfanylation of 3-Ph-cyclobutanone and 2-phenylethyl cyclobutanone.

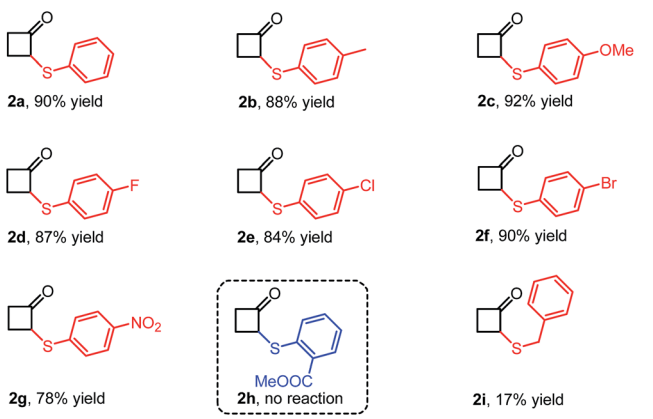
Table 1 α-Sulfanylation of cyclobutanone **1a**. Solvent and temperature screening[a]

Entry	Solvent	Temp/°C	Time/h	Yield[b]/%
1	DMSO	10	24	—
2	DMSO	25	24	18
3	DMSO	50	12	90
4	DMF	25	24	32
5	DMF	50	24	42
6	MeCN	50	24	—
7	MeOH	50	24	15
8	H_2O	50	24	—

[a] Reactions conditions DMSO (1.0 mL), cyclobutanone **1** (250 mg, 3.57 mmol), D,L-proline (20 mol%), diphenyldisulfide (778 mg, 3.57 mmol). [b] Isolated yield.

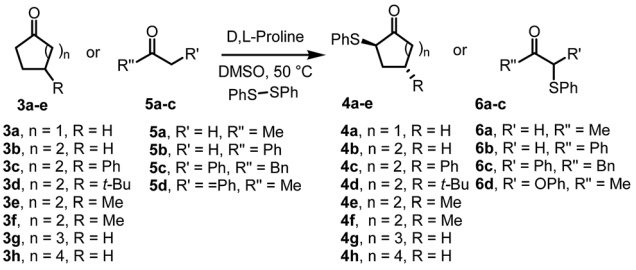
Table 2 α-Sulfanylation of cyclobutanone **1a** with substituted diaryldisulfides[a]

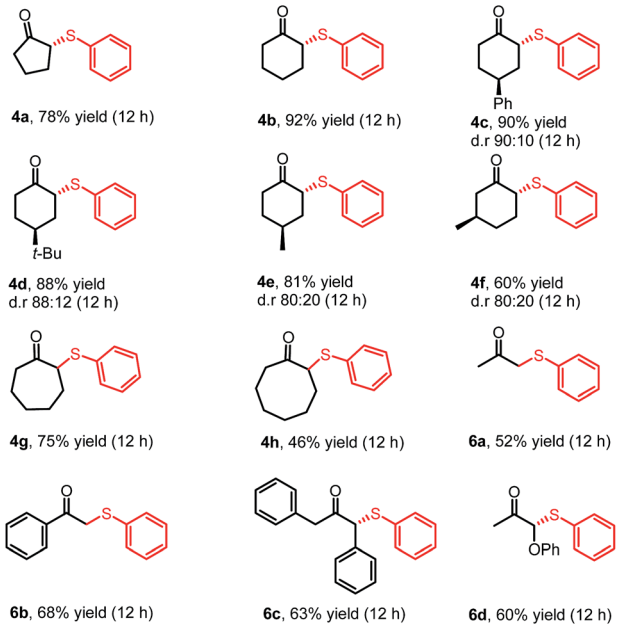




[a] Reactions were carried out in a sealed vial containing DMSO (1.0 mL), cyclobutanone **1** (250 mg, 3.57 mmol), D,L-proline. (20 mol%), aryldisulfide (778 mg, 3.57 mmol) at 50 °C. The reaction mixture was treated with $NaHCO_3$, extracted with Et_2O and dried on Na_2SO_4. The filtered organic phase was concentrated and purified by flash chromatography. Yields are given for isolated materials after column chromatography.

Table 3 D,L-Proline catalyzed α-sulfanylation of cyclic and linear ketones **3a–h** and **5a–d** using diphenyldisulfide[a]



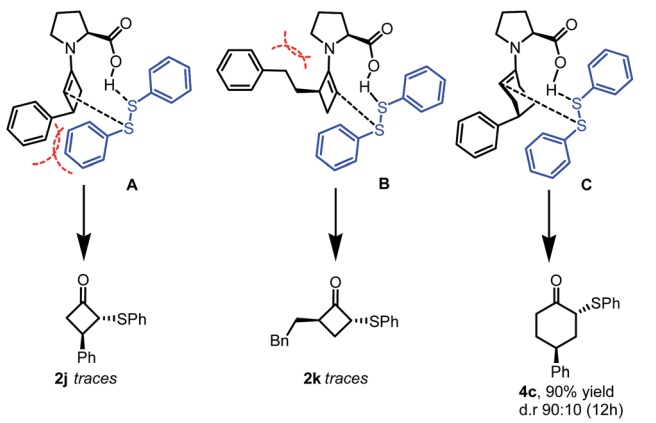


[a] Reactions were carried out in a sealed vial containing DMSO (1.0 mL), ketone **3** or **5** (3.57 mmol), D,L-proline (20 mol%), disulfide (778 mg, 3.57 mmol) at 50 °C. Work-up $Et_2O/NaHCO_3$. Yields are given for isolated materials after column chromatography.

bearing functional groups at the C2 and C3 positions. For this purpose, cyclobutanone **1b** and **1c** were reacted with diphenyldisulfide in the above reported conditions. Moreover, this transformation was not effective and the corresponding reaction product **2j** and **2l** were observed only in traces by GC-MS analysis of the corresponding crude mixtures. The same ketones were also reacted with bis(*n*-decyl)disulfide in order to reduce potential steric-effects induced by the disulfide phenyl-moiety with the introduction of a more flexible alkyl-chain. However, we were not able to observe the formation of the desired reaction products **2k** and **2m**. As reported in the Scheme 2. With the optimized conditions in hands, we wanted to explore the extensibility of this procedure to other ketones. For this reason, a series of cyclic and linear carbonyl compounds were submitted to sulfanylation reaction using our developed protocol. The results of this investigation are reported in Table 3.

Cyclopentanone **3a** and cyclohexanone **3b** were converted into the corresponding ketosulfides in excellent yields after 12 hour reaction (Table 3). 4-*t*Bu-substituted cyclohexanones **3d** was efficiently converted into the corresponding *trans*-α-sulfanyl derivatives **4d** as a 88 : 12 *trans*/*cis* mixture. Similarly, 3-methyl and 4-methyl-(α-sulfanyl)cyclohexanone **4e** and **4f** were recovered in good yields as 80 : 20 *trans*/*cis* mixture of stereoisomers.

Eptanone **3g** and octanone **3h** were also transformed in their corresponding sulfanyl-derivatives in good to acceptable yields. Acyclic ketones, such as acetone, acetofenone and 1,3-diphenyl acetone, were efficiently sulfanylated at the α-position, yielding the corresponding products in good yields. Interestingly, phenoxyacetone **5d** reacted with diphenyldisulfide to yield the corresponding phenylthioketone **6d** with chemoselective functionalization at the C-1 of the starting material. ^{1}H NMR analysis of the crude mixture of this compound, also revealed the formation of the C-3 functionalized regioisomer (19%), easily detectable by the characteristic doublet signals of the C-1 and C-3 bearing respectively a PhO- (δ: 4.65 ppm), and the PhS-group (δ: 3.35 ppm). Experiments carried out with ketone **3c** were also of help for the rationalization of the previously obtained results with 2- and 3-substituted cyclobutanones **1b,c**. As a matter of facts, this reaction can be rationalized by assuming as a model the mechanism shown in Scheme 3, in which the approach of the diaryldisulfide to the enamines is facilitated by the carboxylate function through the formation of a hydrogen-bonding interaction, and the concomitant disposition of the carbocyclic ring enamine-intermediates substituents with a preferential orientation in order to minimize the steric repulsion as evidenced in the proposed transition states **A–C** (Scheme 3). This hypothesis is also supported by further experiments carried out with substituted 2-methyl- and 2-allyl-cyclohexanones. Reactions carried-out with these compounds where ineffective, and the starting materials were recovered unchanged after 48 hours reaction. On the other hand, 3-methyl- and 4-methylcyclohexanone **3f** and **3e** (Table 3), were efficiently converted into their corresponding sulfanyl-derivative. These studies reveal that the formation of the enamine-species are strongly reduced when further substitution is localized in the α-position respect to the cyclohexyl-carbonyl group and that, the formation of a less sterically congested



Scheme 3 α-Sulfanylation of 3-Ph-cyclobutanone **1b**, 2-phenylethyl cyclobutanone **1c** and 4-phenylcyclohexanone **3c**.

reactive enamine intermediate such as **C** are a necessary condition in order to get the α-sulfanylation. This behaviour is peculiar for this reaction. In fact, other electrophiles, such as aromatic aldehydes[12] and nitrosobenzene,[13] have been successfully used for the functionalization of 3-substituted cyclobutanones using pyrrolidine-catalysts with excellent results.[12]

DFT-calculations, were also carried-out with the aim to better understand the reactivity of different disulfide compounds involved in this reaction through the quantum-mechanical calculation of the S atom natural charge.[14] In accordance with the experimental data, charges on S atom, resulted to be lower for aliphatic- (+0.0561) or benzylic disulfides (+0.12628) to respect EDG-functionalized disulfide such as *p*-methoxyphenyldisulfide (+0.17852) or diphenyldisulfide (+0.17848). As expected high charge values were calculated for disulfide derivatives bearing EWG-groups such as *p*-nitrodiphenyldisulfide (+0.19717), summarized in Fig. 1 (for more details see ESI†).

This result can be evoked to rationalize the low reactivity of *n*-alkyl-disulfides such as bis(*n*-decyl)- or bis(benzyl)disulfides as reported in Table 2 and Scheme 2.

With these information in hands, we further explored the scope of this proline-catalyzed sulfanylation by reacting cyclohexanone **3d** with differently substituted aryldisulfides as reported in Table 4.

All the diaryldisulfides used for this survey, well reacted with compound **3d**, under the developed reaction conditions. High diastereoselectivity was observed when disulfides bearing EWD-groups on the aromatic moiety were used. Reactions carried out with bis(4-fluoro)-, bis(4-bromo)- and bis(4-chloro)disulfides afforded the corresponding ketosulfides **7e**, **7f** and **7g** in high yields and good diastereoselectivity.

On the other hand, bis(4-nitro)disulfide gave the corresponding ketosulfide **7h** in high yield after 8 hours reaction but ^{1}H-NMR analysis of the crude reaction mixture revealed lower diastereoselectivity (*trans*/*cis* 78 : 22). Similar results were obtained when bulky bis-(naphthalene)disulfide was reacted with cyclohexanone **3d**, affording the corresponding sulfanyl-adduct **7i** in good yield but the diastereoselectivity resulted to be the lower of the series after 20 hours reaction.

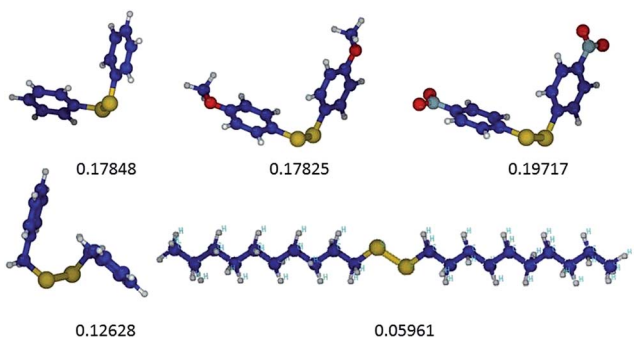
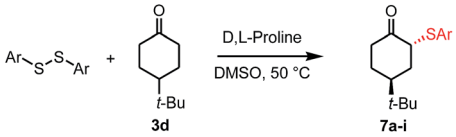
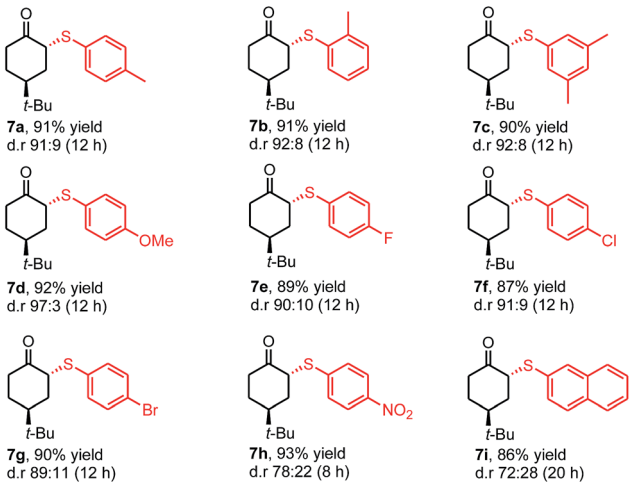


Fig. 1 Ball and stick drawing and atom labelling scheme of the compounds **e**, **g**, **i**, **a**, **l**. DFT level optimized geometry.

Table 4 D,L-Proline catalysed diastereoselective α-sulfanylation of *t*-Bu-cyclohexanone with functionalized aryldisulfides[a]





[a] Reactions were carried out in a sealed vial containing DMSO (1.0 mL), **3d** (3.57 mmol), D,L-proline. (20 mol%), aryl disulfide (3.57 mmol) at 50 °C. Work-up $Et_2O/NaHCO_3$. Yields are given for isolated materials after column chromatography.

Conclusions

Herein, we have reported the development of a new organocatalyzed disulfide-based, metal-free α-sulfanylation-reaction of cyclic and acyclic ketones. This methodology has been performed by using EDG- and EWG-substituted diphenyldisulfide, affording the corresponding reaction products in good to excellent yields and high diastereo-regio-and chemoselectivity. DFT calculations, were performed in order to understand the reactivity of different aromatic- and aliphatic disulfides, disclosing a direct correlation between the natural charge on the S atom and the formation of ketosulfides by direct proline-based sulfanylation reaction. Further studies related to the development of an enantioselective version of this reaction are currently underway.

Experimental section

Unless stated otherwise, reaction were performed at ambient temperature (25 °C). Commercially available reagents were used as received unless otherwise noted. Diphenyldisulfide, *p*-nitrophenyldisulfide, cyclobutanone **1a**, cyclopentanone **3a**, cyclohexanones **3b–f**, other cyclic ketones such as **3g–h** and ketones **5a–d** were purchased from Aldrich. Catalysts I–VII were purchased from Aldrich or Alfa-Aesar and used as received. ^{1}H NMR spectra were recorded on 400 and 500 MHz Varian

spectrometers at 27 °C using $CDCl_3$, DMF-*d*7 or DMSO-*d*6 as solvent. ^{13}C NMR were recorded at 100 and 125 MHz at 27 °C using $CDCl_3$, DMF-*d*7 or DMSO-*d*6 as solvent. Chemical shifts (δ) are given in ppm. Coupling constants (J) are reported in Hz. Infrared spectra were recorded on a FT-IR Bruker Equinox-55 spectrophotometer and are reported in wavenumbers. Low mass spectra analysis were recorded on an Agilent-HP GC-MS (E.I. 70 eV). High resolution mass spectra (HRMS) were obtained using a Bruker High Resolution Mass Spectrometer in fast atom bombardment (FAB+) ionization mode or acquired using an Bruker micrOTOF-Q II 10027.

HPLC analysis were obtained from Hitachi-LaChrome 7100-UV/7400-Pump integrated system and using chiral HPLC columns OJ, OD-H, AD-H and Phenomenex-Lux.

Analytical thin layer chromatography was performed using 0.25 mm Aldrich silica gel 60-F plates. Flash chromatography was performed using Merck 70–200 mesh silica gel. Yields refer to chromatography and spectroscopically pure materials.

Density Functional Theory methods (DFT) were performed on symmetric aromatic and aliphatic disulfides with Gaussian09 (ref. 14) All calculations were carried out with the mPW1PW hybrid functional[15] with the split valence 6-311G[16] basis sets, for all atomic species. NBO populations[17] bond indices were calculated at the optimized geometries, which were verified by harmonic frequency calculations. Tight SCF convergence criteria and fine numerical integration grids were used for all calculations. The results of the calculations were examined with GaussView 5 and Molden 5.0 programs.[18]

General procedure for the synthesis of diphenyldisulfides b–l

Substituted diaryldisulfides **b–l** were synthesized as follow: to a stirred solution of benzenethiol (2.0 g, 16 mmol) in MeOH (50 mL), K_2CO_3 (4.41 g, 32 mmol) and $CuCl_2$ (215 mg, 1.6 mmol) were added and the resulting mixture was bubbled with air for 2–10 hours. The resulting reaction mixture was filtered and the solid was washed with MeOH (2 × 20 mL). The organic phase was washed with a saturated solution of $NaHCO_3$ and dried on Na_2SO_4. After filtration the solution was concentrated under reduced pressure, the crude disulfide was purified by flash chromatography (eluents hexanes–hexanes : diethyl ether 95 : 5) affording the corresponding pure product **b** in 92% yield. White solid, mp 44–45 °C (recrystallized by *n*-hexane). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.36 (d, 4H, J = 5.0 Hz), 7.09 (d, 4H J = 5.0 Hz), 2.31 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.42, 133.89, 129.76, 128.53, 21.04; Ms (EI) *m*/*z*: (%) 246, (25) [M+], 125 (5), 123 (100), 91 (15), 79 (44), 65 (15).[19]

bis(*o*-Tolyl)disulfide c. Yield 91%, yellow oil. FTIR neat, cm^{-1} ν: 3058, 3014, 2973, 1540, 1452, 1035; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.547.48 (m, 1H), 7.17–7.09 (m, 3H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.34, 135.37, 130.27, 128.63, 127.29, 126.64, 19.96; GC-MS (EI) *m*/*z*: (%) 246, (100) [M+], 213 (8), 198 (6), 182 (10), 167 (6), 123 (67), 108 (9), 91 (11), 77 (13). Spectroscopic data are in accordance with the previously presented.[19]

bis(3,5-Dimethylphenyl)disulfide d. Yield 89%, yellow oil. FTIR neat, cm^{-1} ν: 3010, 2921, 2862, 1537, 1459, 1038; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.11 (s, 2H), 6.84 (s, 4H), 2.27 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.67, 136.79, 128.97, 125.12, 21.21; GC-MS (EI) *m*/*z*: (%) 274, (100) [M+], 259 (6), 241 (12), 226 (19), 210 (8), 195 (17), 168 (5), 137 (24), 121 (13), 105 (7), 91 (12), 77 (11). Spectroscopic data are in accordance with the previously presented.[19]

bis(*p*-Methoxyphenyl)disulfide e. Yield 90%, white solid. Mp 75–78 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.22–7.18 (m, 2H), 7.07 (d, 4H, J = 1.1 Hz), 6.76 (dd, 2H, J = 1.1 Hz J = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.8, 132.6, 128.4, 114.5, 55.3; GC-MS (EI) *m*/*z*: (%) 278, (22) [M+], 140 (100), 139 (100), 96 (21), 77 (9). Spectroscopic data are in accordance with the previously presented.[19]

bis(*p*-Fluorophenyl)disulfide f. Yield 91%, colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.43 (dt, 4H, J = 1.2 Hz, J = 2.5 Hz), 7.00 (t, 4H, J = 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.6 (d, J = 308 Hz), 132.1 (d, J = 3.87 Hz), 131.2 (d, J = 10.6 Hz), 116.2 (d, J = 28.0 Hz); GC-MS (EI) *m*/*z*: (%) 254, (77), 128 (100), 96 (33), 75 (12). Spectroscopic data are in accordance with the previously presented.[20]

bis(*p*-Chlorophenyl)disulfide g. Yield 90%, white solid. Mp 71–73 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.40–7.38 (m, 2H), 7.28–7.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.1, 133.6, 129.3, 129.2; GC-MS (EI) *m*/*z*: (%) 288, (13), 287 (23) [M+], 222 (6), 145 (24), 143 (100), 108 (66), 99 (21), 75 (12), 63 (14). Spectroscopic data are in accordance with the previously presented.[19]

bis(*p*-Bromopehnyl)disulfide h. Yield 93%, crystalline white solid. Mp 92–93 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.43–7.41 (m, 4H), 7.34–7.32 (m, 4); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.7, 132.2, 129.4, 121.5; GC-MS (EI) *m*/*z*: (%) 377, (72), 376 (100) [M+], 375 (63), 312 (8), 297 (18), 296 (17), 189 (77), 188 (74), 108 (81), 82 (15), 69 (16). Spectroscopic data are in accordance with the previously presented.[21]

bis(Benzyl)disulfide i. Yield 98%, brown solid. Mp 68–70 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.22 (m, 10H), 3.60 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.3, 129.3, 128.4, 127.3, 43.3. GC-MS (EI) *m*/*z*: (%) 246, (7) [M+], 91 (100), 65 (17). Spectroscopic data are in accordance with the previously presented.[19]

bis(*o*-Carboxymethylpehnyl)disulfide j. Yield 89%, white solid. Mp 196–198 °C; FTIR neat, cm^{-1} ν: 2955, 1718, 1699, 1549, 1456, 1271, 1142, 1105, 1057; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.06 (dd, 1H, J = 1.0 Hz, 10.0 Hz), 7.43–7.27 (m, 1H), 7.26 (d, 1H, J = 10.0 Hz), 7.23 (dd, 1H, J = 10 Hz, J = 20 Hz), 3.99 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.9, 140.3, 133.1, 131.4, 127.3, 125.8, 125.4, 52.4; GC-MS (EI) *m*/*z*: (%) 334, (21), 319 (14), 167 (100), 109 (61), 77 (47%), 65 (39%), 62 (65%). Spectroscopic data are in accordance with the previously presented.[22]

bis(Naphthyl)disulfide k. Yield 93%, beige solid: mp 140–141 °C. ^1H NMR (400 MHz, DMSO-*d*6) δ: 7.23 (s, 2H), 7.05 (d, 2H, J = 8.7 Hz), 6.99 (dd, 4H, J = 9.1 Hz, J = 6.9 Hz), 6.77 (dd, 2H, J = 8.7 Hz, J = 1.8 Hz), 6.66–6.57 (m, 4H); ^{13}C NMR (100 MHz, DMSO-*d*6) δ: 133.1, 133.0, 132.1, 129.3, 127.8, 127.4, 127.1, 126.7, 126.3, 125.3. Spectroscopic data are in accordance with the previously presented.[19]

bis(*n*-decyl)disulfide l. bis(Decyl)disulfide **l**. Yield 96%, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.68 (t, J = 7.4 Hz, 4H), 1.73–1.59 (m, 4H), 1.37 (dd, J = 13.6, 6.7 Hz, 4H), 1.26 (s, 24H), 0.88 (t, J = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 39.4,

32.0, 29.7, 29.6, 29.5, 29.4, 28.7, 22.8, 14.2. Spectroscopic data are in accordance with the previously presented.[23]

General procedure for the α-sulfanylation of ketones

Ketones **2a–i**, **3a–h**, **5a–d** and **7a–i**, were synthesized as follow: In a 5 mL vial, diphenyldisulfide (1 g, 4.5 mmol) cyclobutanone **1a** (315 mg, 4.5 mmol) and D,L-proline (103 mg, 0.9 mmol), in DMSO (2 mL), were stirred for 12 hours at 50 °C. The resulting reaction mixture was diluted with diethyl ether and washed with a saturated solution of $NaHCO_3$. The separated organic phase was dried with Na_2SO_4 and filtered. After concentration under reduced pressure, the crude ketosulfide was purified by flash chromatography (eluent, hexanes : diethyl ether 95 : 5) affording the corresponding pure product **2a** in 90% yield. Colorless oil. FTIR (KBr) cm^{-1} ν: 3000, 1790, 1480, 1440. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.43 (d, 2H, $J = 5.0$ Hz), 7.30–7.24 (m, 3H), 4.49–4.44 (m, 1H), 3.05–2.93 (m, 1H), 2.49–2.46 (m, 1H), 1.95–1.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 204.9, 133.2, 131.5, 128.8, 127.2, 59.2, 44.8, 18.5. GCMS (EI) m/z: (%) 178, (12%) [M+], 155 (4), 149 (7), 136 (100), 135 (78), 121 (13), 115 (9), 109 (14), 91 (22), 77 (9), 65 (10).[5]

2-(4-Methyl-phenylsulfanyl)-cyclobutanone 2b. Yellow oil, 88% yield. FTIR neat, cm^{-1} ν: 2989, 1788, 1556, 1058, 804; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36 (d, $J = 8.0$ Hz, 1H), 7.11 (d, $J = 7.8$ Hz, 1H), 4.41 (ddt, 1H, $J = 9.7$ Hz, $J = 7.1$ Hz, $J = 2.6$ Hz), 3.03 (dddd, 1H, $J = 18.0$ Hz, $J = 10.3$ Hz, $J = 7.8$ Hz, $J = 2.6$ Hz), 2.96–2.82 (m, 1H), 2.55–2.38 (m, 1H), 2.32 (s, 2H), 1.99–1.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.4, 137.9, 132.9, 129.7, 129.1, 59.9, 44.9, 21.0, 18.5; GC-MS (EI) m/z: (%) 170, (28) [M+], 146 (100), 128 (73), 123 (80), 91 (65), 65 (15).[5]

2-(4-Methoxy-phenylsulfanyl)-cyclobutanone 2c. Yellow oil, 92% yield. FTIR neat, cm^{-1} ν: 3010, 2958, 2840, 1789, 1588, 1474, 1282, 1249, 1072, 1038. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.20 (dd, 1H, $J = 10.0$ Hz, $J = 6.3$ Hz), 7.01 (dt, 2H, $J = 11.9$ Hz, $J = 6.3$ Hz), 6.82–6.77 (m, 1H), 4.53–4.44 (m, 1H), 3.79 (s, 1H), 3.14–3.04 (m, 1H), 3.04–2.94 (m, 1H), 2.51 (ddd, 1H, $J = 21.2$ Hz, $J = 10.4$ Hz, $J = 6.0$ Hz), 1.95 (ddt, 1H, $J = 10.6$ Hz, $J = 9.5$ Hz, $J = 7.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.15, 159.86, 134.79, 129.86, 129.73, 127.05, 123.72, 119.88, 116.80, 115.35, 113.51, 59.45, 55.36, 45.13, 18.85; GC-MS (EI) m/z: (%) 208 (19) [M+], 179 (7), 166 (100), 165 (54), 150 (22), 135 (42), 121 (33), 108 (9), 96 (12), 77 (10), 69 (8), 45 (11), 39 (13). Spectroscopic data are in accordance with the previously presented.[5]

2-(4-Fluoro-phenylsulfanyl)-cyclobutanone 2d. Colorless oil, 87% yield. FTIR neat, cm^{-1} ν: 3003, 1790; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.51–7.44 (m, 1H), 7.04–6.96 (m, 1H), 4.40 (ddt, 1H, $J = 9.9$ Hz, $J = 7.2$ Hz, $J = 2.7$ Hz), 3.06 (dddd, 1H, $J = 18.0$ Hz, $J = 10.4$ Hz, $J = 7.7$ Hz, $J = 2.7$ Hz), 2.99–2.85 (m, 1H), 2.48 (dtd, 1H, $J = 11.9$ Hz, $J = 10.2$ Hz, $J = 5.9$ Hz), 1.98–1.83 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 205.2, 163.8, 161.8, 135.4, 135.3, 128.0, 116.3, 116.2, 60.2, 45.1, 18.5; GC-MS (EI) m/z: (%) 196 (11) [M+], 154 (100), 139 (12), 127 (18), 109 (27), 83 (20), 57 (6), 41 (8); HRMS (ESI): calcd for $C_{10}H_9FNaOS$: 219.2310 ($M + Na^+$), found: 219.2314.

2-(4-Chloro-phenylsulfanyl)-cyclobutanone 2e. Yellow oil, 84% yield. FTIR neat, cm^{-1} ν: 2966, 2954, 1789; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.48–7.20 (m, 4H), 4.32 (t, 1H, $J = 6.8$ Hz), 3.20–2.84 (m, 2H), 2.70–2.22 (m, 1H), 2.04–1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.75, 136.61, 133.53, 132.70, 132.29, 132.22, 121.92, 59.38, 45.22, 18.67. Spectroscopic data are in accordance with the previously presented.[5]

2-(4-Bromo-phenylsulfanyl)-cyclobutanone 2f. Pale yellow solid, 90% yield. Mp 44–45 °C, FTIR (KBr) cm^{-1} ν: 2958, 2901, 1790; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, 1H, $J = 8.3$ Hz), 7.29 (d, 1H, $J = 8.4$ Hz), 4.49–4.37 (m, 1H), 3.16–2.88 (m, 1H), 2.55–2.39 (m, 1H), 1.98–1.82 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 204.75, 136.61, 133.53, 132.70, 132.29, 132.22, 121.92, 59.38, 45.22, 18.67; GC-MS (EI) m/z: (%) 258 (12), 256 (10), 216 (100), 214 (96), 189 (10), 187 (8), 171 (11), 169 (9), 149 (12), 135 (80), 134 (38), 116 (13), 108 (27), 91 (18), 69 (10); HRMS (ESI): calcd for $C_{10}H_9BrNaOS$: 278.9455 ($M + Na^+$), found: 278.9456.

2-(4-Nitro-phenylsulfanyl)-cyclobutanone 2g. Yellow deliquescent solid, 78% yield. FTIR (KBr) cm^{-1} ν: 2981, 2683, 1789, 1658, 1462, 1325; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.12–8.03 (m, 1H), 7.49–7.39 (m, 1H), 4.72–4.61 (m, 1H), 3.29–3.14 (m, 1H), 2.68–2.54 (m, 1H), 2.04–1.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.1, 145.8, 144.7, 130.5, 128.0, 123.9, 57.1, 45.5, 18.4; GC-MS (EI) m/z: (%) 223, (7) [M+], 207 (6), 181 (100), 164 (13), 147 (11), 138 (82), 121 (9), 115 (11), 107 (21), 91 (39), 82 (19), 75 (10), 69 (27), 45 (34), 39 (37); HRMS (ESI): calcd for $C_{10}H_9NNaO_3S$: 246.0201 ($M + Na^+$), found: 246.0204.

2-Phenylsulfanyl-cyclopentanone 4a. Yellow oil, 78% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.46–7.41 (m, 1H), 7.29–7.21 (m, 2H), 3.53 (t, 1H, $J = 7.0$ Hz), 2.38–2.16 (m, 2H), 2.10–1.98 (m, 1H), 1.97–1.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.90, 133.55, 132.65, 129.10, 127.85, 52.49, 36.70, 30.77, 20.45; GC-MS (EI) m/z: (%) 192, (100) [M+], 164 (6), 136 (91), 109 (16), 91 (20), 65 (11). Spectroscopic data are in accordance with the previously presented.[24]

2-Phenylsulfanyl-cyclohexanone 4b. Yellow oil, 92% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39–7.33 (m, 1H), 7.21 (ddd, 2H, $J = 14.2$ Hz, $J = 11.0$ Hz, $J = 3.7$ Hz), 3.78 (t, 1H, $J = 5.8$ Hz), 2.87 (ddd, 1H, $J = 14.3$ Hz, $J = 9.3$ Hz, $J = 5.4$ Hz), 2.33–2.11 (m, 2H), 2.03 (ddd, 1H, $J = 13.9$ Hz, $J = 5.9$ Hz, $J = 4.0$ Hz), 1.96–1.85 (m, 2H), 1.84–1.72 (m, 1H), 1.71–1.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.73, 133.98, 132.02, 129.15, 127.56, 56.58, 42.11, 39.18, 34.09, 27.48, 27.14, 25.13, 22.74; GC-MS (EI) m/z: (%) 206 (87) [M+], 178 (9), 162 (16), 135 (11), 110 (100), 91 (9), 69 (13). Spectroscopic data are in accordance with the previously presented.[24]

4-*tert*-Butyl-2-phenylsulfanyl-cyclohexanone 4d. Yellow oil, 88% yield (90 : 10). Major isomer (*trans*) FTIR neat, cm^{-1} ν: 3062, 2958, 2870, 1718, 1478, 1371, 1219, 1168, 1086, 1024; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.32 (m, 3H), 7.26–7.16 (m, 2H), 3.07 (td, 1H, $J = 14.2$ Hz, $J = 6.1$ Hz), 2.40–2.29 (m, 2H), 2.28–2.20 (m, 2H), 2.04 (ddd, 1H, $J = 10.0$ Hz, $J = 6.8$ Hz, $J = 2.7$ Hz), 1.83 (qdd, 1H, $J = 18.5$ Hz, $J = 14.2$ Hz, $J = 5.8$ Hz), 1.46–1.31 (m, 1H), 0.87 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.7, 132.1, 131.6, 129.2, 127.7, 54.9, 46.8, 41.5, 36.8, 34.0, 32.6, 27.7; GC-MS (EI) m/z: (%) 262, (100) [M+], 205 (21), 177 (11), 153 (11), 135 (20), 110 (41), 95 (16), 57 (32).

Minor isomer (*cis*) ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.32 (m, 3H), 7.24–7.19 (m, 2H), 3.94–3.85 (m, 1H), 2.58–2.49 (m,

1H), 2.30–2.27 (m, 2H), 2.20–2.14 (m, 2H), 1.57–1.46 (m, 2H), 0.83 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.88, 134.1, 132.1, 129.0, 127.2, 57.7, 47.6, 41.8, 36.5, 32.4, 28.1, 27.6. Spectroscopic data are in accordance with the previously presented.[25]

4-Methyl-2-phenylsulfanyl-cyclohexanone 4e. Yellow oil, 81% yield (88 : 12). Major isomer (*trans*) FTIR neat, cm^{-1} 2962, 2929, 2866, 1718, 1540, 1456, 1127, 1027; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39 (dd, 1H, J = 12.4 Hz, J = 8.0 Hz), 7.30–7.20 (m, 2H), 3.76–3.68 (m, 1H), 3.14 (td, 1H, J = 14.0 Hz, J = 6.1 Hz), 2.23 (dddd, 1H, J = 19.8 Hz, J = 8.8 Hz, J = 5.6 Hz, J = 2.8 Hz), 2.08–1.93 (m, 1H), 1.88 (ddd, 1H, J = 14.5 Hz, J = 12.5 Hz, J = 4.8 Hz), 1.45–1.33 (m, 1H), 1.00 (d, 1H, J = 6.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 208.4, 132.6, 131.4, 129.1, 127.6, 54.6, 40.9, 36.4, 35.2, 27.2, 21.2; GC-MS (EI) *m*/*z*: (%) 220, (98) [M+], 192 (6), 177 (8), 163 (11), 135 (18), 110 (100), 83 (14), 69 (10), 55 (34).

Minor isomer (*cis*) ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42–7.39 (m, 2H), 7.25–7.20 (m, 3H), 3.96 (dt, 1H, J = 21.6 Hz, J = 10.9 Hz), 2.57–2.50 (m, 1H), 2.44 (td, 1H, J = 13.8 Hz, J = 6.0 Hz), 2.37–2.29 (m, 2H), 1.56–1.44 (m, 3H), 0.97 (d, 3H, J = 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 208.6, 134.1, 132.6, 129.0, 127.3, 57.5, 43.3, 41.2, 35.4, 34.8, 32.5, 21.0. Spectroscopic data are in accordance with the previously presented.[26]

3-Methyl-2-phenylsulfanyl-cyclohexanone 4f. Yellow oil, 60% yield (80 : 20). Major isomer (*trans*) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.34 (m, 1H), 7.27–7.18 (m, 2H), 3.71–3.67 (m, 1H), 2.75 (dd, J = 13.7, 12.2 Hz, 1H), 2.24–2.16 (m, 2H), 2.15–2.04 (m, 1H), 1.92–1.81 (m, 1H), 1.66 (dd, J = 9.9, 4.0 Hz, 2H), 1.14 (dd, J = 21.6, 6.9 Hz, 1H), 1.01 (d, J = 6.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 208.1, 161.3, 131.5, 129.2, 127.6, 54.5, 45.5, 34.8, 31.7, 29.4, 22.1; GC-MS (EI) *m*/*z*: (%) 220, (96) [M+], 192 (13), 149 (37), 135 (16), 110 (100), 83 (15), 69 (13), 55 (31). Spectroscopic data are in accordance with the previously presented.[27]

2-Phenylsulfanyl-cycloheptanone 4g. Yellow oil, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46–7.31 (m, 1H), 7.25 (tdd, J = 6.9, 4.6, 2.2 Hz, 1H), 3.75 (dd, J = 10.6, 5.5 Hz, 1H), 2.83–2.67 (m, 1H), 2.52–2.42 (m, 1H), 2.37 (ddd, J = 13.0, 7.2, 2.6 Hz, 1H), 2.29–2.15 (m, 1H), 2.00–1.83 (m, 1H), 1.83–1.73 (m, 1H), 1.73–1.54 (m, 1H), 1.54–1.39 (m, 1H), 1.39–1.23 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 209.0, 133.9, 132.0, 129.1, 127.6, 57.5, 40.1, 30.5, 30.0, 27.2, 25.58; GC-MS (EI) *m*/*z*: (%) 220, (78) [M+], 185 (27), 154 (28), 135 (18), 110 (100), 69 (13), 55 (30). Spectroscopic data are in accordance with the previously presented.[25]

2-Phenylsulfanyl-cyclooctanone 4h. Yellow oil, 46% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (dd, J = 8.0, 1.6 Hz, 1H), 7.25–7.10 (m, 2H), 3.66–3.52 (m, 1H), 2.77 (td, J = 12.4, 3.8 Hz, 1H), 2.18–2.11 (m, 1H), 2.04–1.97 (m, 2H), 1.84–1.76 (m, 1H), 1.69–1.58 (m, 3H), 1.57–1.46 (m, 3H), 1.34–1.23 (m, 2H), 1.19–1.07 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.3, 133.2, 132.7, 129.1, 128.0, 57.8, 37.3, 29.0, 28.6, 27.0, 25.8, 24.5; GC-MS (EI) *m*/*z*: (%) 234, (100) [M+], 149 (42), 135 (16), 123 (13), 110 (92), 69 (10), 55 (34). Spectroscopic data are in accordance with the previously presented.[28]

1-Phenylsulfanyl-propan-2-one 6a. Yellow oil, 52% yield. FTIR neat, cm^{-1} 3058, 3006, 2918, 1714, 1581, 1481, 1441, 1356, 1230, 1153, 1090; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31–7.20 (m, 3H), 7.17 (ddd, 1H, J = 7.1 Hz, J = 3.7 Hz, J = 1.2 Hz), 3.62 (s, 1H), 2.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.60, 134.08, 129.60, 129.25, 126.98, 44.75, 28.08; GC-MS (EI) *m*/*z*: (%) 166, (75) [M+], 123 (100), 109 (17), 91 (8), 77 (15), 45 (30). Spectroscopic data are in accordance with the previously presented.[29]

1-Phenyl-2-phenylsulfanyl-ethanone 6b. Yellow oil, 68% yield. FTIR neat, cm^{-1} 3062, 2903, 2681, 1696, 1577, 1484, 1448, 1278, 1201, 1012; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (dd, 2H, J = 8.4 Hz, J = 1.2 Hz), 7.59–7.49 (m, 1H), 7.42 (t, 2H, J = 7.8 Hz), 7.36 (dd, 2H, J = 5.2 Hz, J = 3.2 Hz), 7.24 (tt, 2H, J = 8.5 Hz, J = 1.9 Hz), 7.21–7.17 (m, 2H), 4.24 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.15, 135.48, 134.87, 133.56, 130.59, 129.16, 128.77, 127.19, 41.31; GC-MS (EI) *m*/*z*: (%) 228, (44) [M+], 123 (12), 105 (100), 91 (7), 77 (32), 51 (9). Spectroscopic data are in accordance with the previously presented.[9a]

1,3-Diphenyl-1-phenylsulfanyl-propan-2-one 6c. White solid, 63% yield. FTIR neat, cm^{-1} 3065, 3028, 1718, 1540, 1492, 1456, 1219, 1049, 909; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.27 (m, 6H), 7.26–7.17 (m, 7H), 7.00 (dd, 2H, J = 7.3 Hz, J = 1.9 Hz), 5.08 (s, 1H), 3.74 (ABq, 2H, J = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.23, 135.36, 133.74, 133.67, 132.63, 129.65, 129.08, 129.02, 128.92, 128.74, 128.42, 127.92, 127.18, 62.87, 47.36; GC-MS (EI) *m*/*z*: (%) 318, (9) [M+], 199 (100), 165 (12), 121 (7), 91 (24). Spectroscopic data are in accordance with the previously presented.[30]

1-Phenoxy-1-phenylsulfanyl-propan-2-one 6d. Yellow oil, 60% yield. FTIR neat, cm^{-1} ν: 3005, 2988, 1748, 1216; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48–7.44 (m, 2H), 7.33–7.28 (m, 6H), 7.03–6.99 (m, 2H), 5.72 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.45, 155.85, 134.74, 129.99, 129.82, 129.70, 129.28, 122.93, 116.81, 116.24, 114.62, 87.57, 26.29.204.6, 47.2, 32.1; GC-MS (EI) *m*/*z*: (%) 258, (7) [M+], 215 (100), 184 (5), 165 (43), 147 (14), 132 (18), 121 (16), 109 (34), 94 (6), 77 (35), 65 (11).

4-*tert*-Butyl-2-(4-methylphenylsulfanyl)-cyclohexanone 7a. Yellow oil, 91% yield (91 : 9). Major isomer (*trans*) FTIR neat, cm^{-1} ν: 2962, 2870, 1707, 1540, 1489, 1371, 1263, 1223; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, 2H, J = 8.1 Hz), 7.09 (d, 2H, J = 8.1 Hz), 3.68–3.65 (m, 1H), 3.12 (td, 1H, J = 14.2 Hz, J = 6.1 Hz), 2.31 (s, 3H), 2.29–2.20 (m, 2H), 2.09 (ddt, 1H, J = 12.1 Hz, J = 5.7 Hz, J = 2.7 Hz), 1.96–1.81 (m, 2H), 1.44 (ddd, 1H, J = 25.0 Hz, J = 13.5 Hz, J = 4.1 Hz), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.06, 137.6, 132.1, 129.9, 129.6, 55.2, 41.3, 36.3, 33.4, 31.9, 27.7, 27.3, 20.9; GC-MS (EI) *m*/*z*: (%) 276, (100) [M+], 219 (14), 201 (7), 150 (8), 137 (19), 124 (68), 105 (6), 91 (12), 69 (10); HRMS (ESI): calcd for $C_{17}H_{24}NaOS$: 299.1446 (M + Na^+), found: 299.1448.

4-*tert*-Butyl-2-(2-methylphenylsulfanyl)-cyclohexanone 7b. Yellow oil, 91% yield (92 : 8). Major isomer (*trans*) FTIR neat, cm^{-1} ν: 2962, 2870, 2257, 1710, 1474, 1219; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46–7.37 (m, 1H), 7.20–7.10 (m, 3H), 3.67 (dd, 1H, J = 3.8 Hz, J = 1.9 Hz), 3.12 (td, 1H, J = 14.2, J = 6.1 Hz), 2.41 (s, 3H), 2.27 (dddd, 2H, J = 8.4, J = 6.1 Hz, J = 5.1 Hz, J = 2.8 Hz), 2.10 (ddd, 1H, J = 12.5, 5.8, 2.9 Hz), 2.01–1.84 (m, 2H), 1.52–1.35 (m, 1H), 0.93 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.4, 139.5, 133.0, 132.4, 130.3, 127.7, 126.6, 54.0, 41.6, 36.7, 33.9, 32.2, 27.9, 27.4, 20.6; GC-MS (EI) *m*/*z*: (%) 276, (100) [M+], 243 (6), 219 (14), 201 (9), 153 (7), 137 (12), 124 (36), 109 (5), 91 (11), 69 (12); HRMS (ESI): calcd for $C_{17}H_{24}NaOS$: 299.1446 (M + Na^+), found: 299.1439.

4-*tert*-Butyl-2-(3,5-dimethylphenylsulfanyl)-cyclohexanone 7c. Yellow oil, 90% yield (92 : 8). Major isomer (*trans*) FTIR neat, cm^{-1} ν: 2962, 2866, 1714, 1474, 1367, 1216, 1142; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.02 (s, 2H), 6.86 (s, 1H), 3.72–3.68 (m, 1H), 3.11 (td, 1H, J = 14.2 Hz, J = 6.1 Hz), 2.27 (s, 6H), 2.33–2.18 (m, 2H), 2.14–2.03 (m, 1H), 1.96–1.80 (m, 2H), 1.50–1.39 (m, 1H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.7, 138.6, 133.3, 129.5, 129.3, 54.9, 41.6, 36.6 (s), 33.9, 32.2, 27.9, 27.4, 21.1; GC-MS (EI) *m*/*z*: (%) 290, (100) [M+], 233 (17), 215 (14), 163 (8), 151 (13), 138 (71), 129 (8), 105 (24), 91 (9), 69 (12); HRMS (ESI): calcd for $C_{18}H_{26}NaOS$: 313.1602 (M + Na^+), found: 313.1607.

4-*tert*-Butyl-2-(4-methoxyphenylsulfanyl)cyclohexanone 7d. Yellow oil, 92% yield (97 : 3). Major isomer (*trans*) FTIR neat, cm^{-1} ν: 3014, 2958, 2836, 1721, 1592, 1492, 1289, 1245, 1171, 1024; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, 2H, J = 8.7 Hz), 6.78 (d, 2H, J = 8.7 Hz), 3.74 (s, 3H), 3.08 (td, 1H, J = 14.3 Hz, J = 6.1 Hz), 2.29–2.16 (m, 2H), 2.10–1.98 (m, 2H), 1.90–1.75 (m, 1H), 1.49–1.31 (m, 2H), 0.88 (s, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.53, 159.94, 135.09, 123.95, 114.74, 56.47, 55.27, 41.47, 36.59, 33.48, 27.86, 27.48; GC-MS (EI) *m*/*z*: (%) 292, (100) [M+], 278 (8), 235 (11), 217 (9), 166 (7), 153 (9), 140 (74), 125 (10), 108 (8), 95 (8); HRMS (ESI): calcd for $C_{17}H_{24}NaO_2S$: 315.1395 (M + Na^+), found: 315.1399.[30]

4-*tert*-Butyl-2-(4-fluorophenylsulfanyl)cyclohexanone 7e. Yellow oil, 89% yield (90 : 10). Major isomer (*trans*) FTIR neat, cm^{-1} ν: 2966, 2870, 2257, 1710, 1492, 1230, 1160; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (dd, 2H, J = 8.7 Hz, J = 5.3 Hz), 6.99 (t, 2H, J = 8.6 Hz), 3.67–3.59 (m, 1H), 3.10 (td, 1H, J = 14.3 Hz, J = 6.1 Hz), 2.27 (ddd, 2H, J = 14.9 Hz, J = 8.5 Hz, J = 2.3 Hz), 2.10 (ddd, 1H, J = 12.5 Hz, J = 5.9 Hz, J = 2.9 Hz), 1.93 (td, 1H, J = 13.0 Hz, J = 4.6 Hz), 1.88–1.79 (m, 1H), 1.57 (d, 1H, J = 16.6 Hz), 1.53–1.38 (m, 1H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.5, 164.1, 134.7 (d, J = 8.4 Hz), 116.45 (d, J = 21.9 Hz), 55.9, 41.8, 36.7, 33.8, 32.4, 28.0, 27.6; GC-MS (EI) *m*/*z*: (%) 280, (100) [M+], 223 (21), 195 (7), 153 (13), 141 (16), 128 (31), 109 (14), 95 (14), 83 (18), 69 (27); HRMS (ESI): calcd for $C_{16}H_{21}FNaOS$: 303.1195 (M + Na^+), found: 303.1198.

Minor isomer (*cis*) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.41 (m, 2H), 6.99 (t, 2H, J = 8.6 Hz), 3.83 (dd, 1H, J = 12.1 Hz, 5.8 Hz), 2.62–2.53 (m, 1H), 2.42–2.33 (m, 2H), 1.54 (dd, 1H, J = 22.5 Hz, 12.9 Hz), 1.34–1.12 (m, 1H), 0.88 (s, 9H); ^{13}C NMR (100 MHz, CDC_3) δ 206.9, 161.3 (d, J = 62.3 Hz), 135.5 (d, J = 8.0 Hz), 116.1 (d, J = 21.8 Hz), 58.5, 47.6, 41.2, 36.4, 32.8, 28.3, 27.5.

4-*tert*-Butyl-2-(4-chlorophenylsulfanyl)cyclohexanone 7f. Yellow oil, 87% yield (91 : 9). Major isomer (*trans*) FTIR neat, cm^{-1} ν: 2962, 2866, 1714, 1540, 1474, 1090, 1005; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, 2H, J = 8.5 Hz), 7.20 (d, 2H, J = 8.5 Hz), 3.04 (td, 1H, J = 14.3, J = 6.1 Hz, 1H), 2.30–2.15 (m, 2H), 2.06 (dtd, 1H, J = 12.3, J = 6.1, J = 3.0 Hz), 1.96–1.83 (m, 1H), 1.78 (tt, 1H, J = 12.5, J = 2.8 Hz), 1.54 (ddd, 1H, J = 26.3, J = 12.2, J = 7.5 Hz), 1.46–1.34 (m, 1H), 0.88 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.3, 133.7, 132.7, 132.4, 129.2, 54.8, 41.7, 36.5, 33.7, 32.2, 27.8, 27.4; GC-MS (EI) *m*/*z*: (%) 298 (42), 297 (29), 296, (100) [M+], 239 (16), 211 (9), 196 (5), 170 (8), 157 (15), 144 (24), 125 (9), 108 (13), 95 (11); HRMS (ESI): calcd for $C_{16}H_{21}ClNaOS$: 319.0899 (M + Na^+), found: 319.0901.

Minor isomer (*cis*) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.28 (m, 2H), 7.21–7.20 (m, 2H), 3.85 (dd, 1H, J = 12.1, 5.3 Hz), 3.69–3.62 (m, 2H), 2.58–2.50 (m, 1H), 2.34 (ddd, 2H, J = 10.1, 8.2, 4.6 Hz), 1.32–1.18 (m, 1H), 1.16–1.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.7, 133.9, 133.6, 133.5, 129.2, 57.9, 47.6, 41.2, 36.3, 32.8, 29.2, 28.3, 27.7.

4-*tert*-Butyl-2-(4-bromophenylsulfanyl)cyclohexanone 7g. Yellow oil, 90% yield (89 : 11). Major isomer (*trans*) FTIR neat, cm^{-1} ν: 2966, 2870, 1714, 1474, 1367, 1223, 1142, 1090, 1068, 100; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, 2H, J = 8.5 Hz), 7.19 (d, 2H, J = 8.5), 3.02 (td, 1H, J = 14.3 Hz, J = 6.1 Hz), 2.28–2.16 (m, 2H), 2.08–2.00 (m, 1H), 1.94–1.83 (m, 1H), 1.77 (tt, 1H, J = 12.5 Hz, J = 2.8 Hz), 1.59–1.46 (m, 1H), 1.39 (ddd, 1H, J = 17.2 Hz, J = 11.2 Hz, 4.1 Hz), 0.87 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 133.3, 132.8, 132.1, 121.7, 54.6, 41.8, 36.5, 33.8, 32.2, 27.9, 27.5, 22.7; GC-MS (EI) *m*/*z*: (%) 344 (7), 343 (24), 342, (100) [M+], 340 (87), 287 (4), 286 (6), 285 (18), 284 (16), 255 (6), 240 (4), 214 (4), 214 (4), 203 (11), 201 (13), 190 (22), 189 (17), 188 (20), 176 (8), 147 (11), 135 (13), 122 (11), 108 (19), 95 (13); HRMS (ESI): calcd for $C_{16}H_{21}BrNaOS$: 363.0394 (M + Na^+), found: 363.0395.

Minor isomer (*cis*) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, 2H, J = 8.5 Hz), 7.19 (d, 2H, J = 8.5 Hz), 3.86 (dd, 1H, J = 12.2 Hz, J = 5.2 Hz), 3.67–3.64 (m, 2H), 2.57–2.47 (m, 1H), 2.39–2.28 (m, 2H), 2.04 (dtd, 1H, J = 9.1 Hz, J = 6.1 Hz, J = 3.0 Hz), 1.29–1.04 (m, 1H), 0.83 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 133.5, 133.4, 131.9, 121.2, 57.5, 47.4, 41.1, 36.2, 32.6, 28.2, 27.6, 11.5.

4-*tert*-Butyl-2-(4-nitrophenylsulfanyl)-cyclohexanone 7h. Orange oil, 93% yield (78 : 22). Major isomer (*trans*) FTIR neat, cm^{-1} ν: 2966, 1710, 1518, 1341; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, 2H, J = 8.9 Hz), 7.48 (d, 2H, J = 8.9 Hz), 3.98–3.92 (m, 1H), 3.06 (td, 1H, J = 14.2 Hz, J = 6.1 Hz), 2.39–2.27 (m, 2H), 2.18–2.11 (m, 1H), 2.10–2.00 (m, 1H), 1.58–1.43 (m, 2H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, CDC_3) δ: 208.0, 144.6, 131.1, 127.9, 123.9, 52.2, 42.1, 36.5, 33.9, 32.2, 27.9, 27.4; GC-MS (EI) *m*/*z*: (%) 307, (100) [M+], 292 (5), 267 (8), 250 (19), 234 (14), 223 (11), 206 (9), 157 (12), 137 (7), 95 (13); HRMS (ESI): calcd for $C_{16}H_{21}NNaO_3S$: 330.1140 (M + Na^+), found: 330.1142.

Minor isomer (*cis*) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (d, 2H, J = 8.9 Hz), 7.32 (d, 2H, J = 8.9 Hz), 4.16 (dd, 1H, J = 12.9 Hz, J = 5.2 Hz), 2.67 (ddd, 1H, J = 14.0 Hz, J = 4.1 Hz, J = 2.9 Hz), 2.55–2.43 (m, 2H), 1.81 (ddd, 2H, J = 12.6 Hz, J = 7.7 Hz, J = 2.8 Hz), 1.70 (ddd, 2H, J = 19.7 Hz, J = 11.3 Hz, J = 4.2 Hz), 1.63–1.59 (m, 1H), 0.93 (s, 9H); ^{13}C NMR (100 MHz, CDC_3) δ: 205.3, 145.8, 128.1, 126.3, 123.9, 55.8, 47.6, 41.0, 35.6, 32.6, 28.1, 27.5; GC-MS (EI) *m*/*z*: 307, (100) [M+], 292 (7), 267 (7), 250 (21), 234 (17), 223 (10), 206 (11), 157 (12), 137 (8), 95 (11).

4-*tert*-Butyl-2-(naphthalen-2-ylsulfanyl)-cyclohexanone 7i. Pale yellow solid, 88% yield (72 : 28). Mp 71–73 °C, major isomer (*trans*) FTIR neat, cm^{-1} ν: 3064, 2958, 2870, 2253, 1714, 1367, 1219, 1134; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (s, 1H), 7.77–7.71 (m, 3H), 7.48–7.39 (m, 3H), 3.87–3.84 (m, 1H), 3.14 (td, 1H, J = 14.2 Hz, J = 6.1 Hz), 2.35–2.23 (m, 2H), 2.10 (ddd, 1H, J = 9.3 Hz, J = 5.9 Hz, 3.0 Hz), 1.99–1.85 (m, 2H), 1.49–1.40 (m, 1H), 0.92 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.68, 133.73, 132.51, 131.42, 130.33, 128.77, 128.76, 127.76, 127.59, 126.62, 126.36, 54.78, 41.85, 41.38, 36.81, 34.00, 32.32, 28.07, 27.69, 27.66, 27.59; GC-MS (EI) *m*/*z*: (%) 312, (100) [M+], 279 (11),

255 (12), 237 (13), 185 (8), 173 (10); HRMS (ESI): calcd for $C_{20}H_{24}NaOS$: 335.1446 (M + Na^+), found: 335.1449.

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