Insights into the reactivity of 2-hydroxycyclobutanones with thiols corroborated by quantum chemical DFT investigations, NMR and Raman analysis

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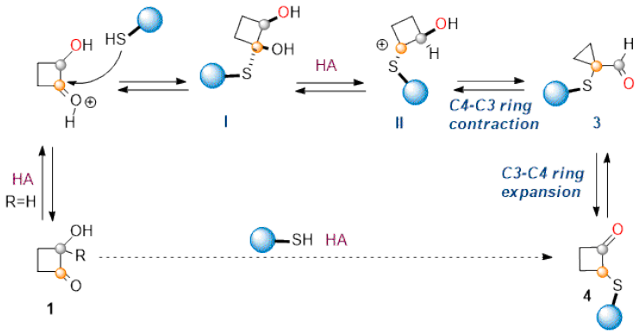

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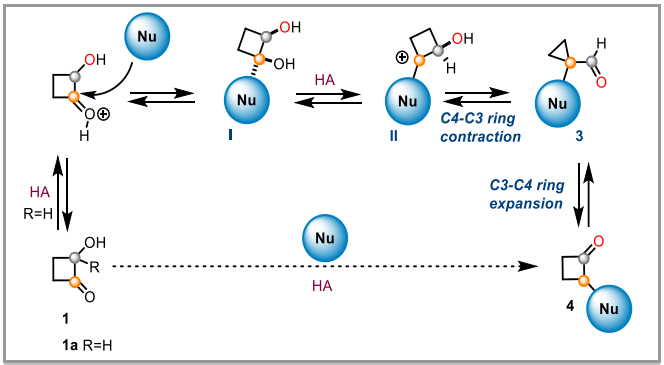
Abstract A general strategy for the synthesis of 2-substituted cyclobutanone sulphides via a tandem Brønsted acid catalysed nucleophile addition/ring-contraction/C3-C4 ring-expansion reaction sequence has been exploited. The procedure led to a wide panel of four membered cyclic ketones in good to excellent yields and with broad substrate scope. Mechanistic aspects and kinetic parameters were investigated by quantum chemical DFT calculations allowing us to rationalize the different reactivity of 2-aryl- and 2-alkyl-substituted 2-hydroxycyclobutanones towards thiol nucleophiles in reactions mediated by sulphonic acids. NMR and in situ Raman techniques, were employed to better understand the reaction kinetics and parameters that affect the desired outcome.

Key words Cyclobutanones, thiols, ring-contraction, ring-expansion, Brønsted acid catalysis, transposition, quantum chemical DFT

Due to the ease of preparation[1] and extensive chemical reactivity,[2] 2-hydroxycyclobutanones **1** constitute a powerful building block for organic synthesis. These cyclic ketones have recently been used for the preparation of benzofuran[3] and tryptamine derivatives,[4] the synthesis of cyclopropane- and cyclobutane-adducts *via* the addition of different nucleophiles such as phosphonium ylides,[5] indoles[6] or aromatic thiols[7]. Furthermore, acid catalysed reaction of 2-hydroxycyclobutanones with benzylic alcohols allows access to bis(cyclobutyl)dioxin derivatives.[8] Stereo- and enantioselective organocatalytic reactions involving cyclic ketone **1** have allowed access to cyclobutane aldol adducts[9] and to developing new and elegant α-amination procedures.[10] All of these applications underline the synthetic value of the hydroxycyclobutanone moiety in organic synthesis.[11] Recently, we undertook studies on the preparation, the reactivity and synthetic applications of arylthiocyclobutanones as a platform for the development of organocatalytic deracemization procedures.[12] For this purpose, a useful synthesis of four membered ring ketones was achieved *via* α-sulfenylation of cyclobutanones using diaryl disulfides.[13]

Lately, we reported that hydroxycyclobutanone **1a** could be easily converted into the corresponding arylthio-carbaldehydes **3** through a tandem acid-catalysed arylthiol-addition/C4-C3 ring-contraction reaction.[7] On the other hand, during this study we observed that reactions of alkylthiols with **1a** allowed the isolation of the related 2-alkylthio-cyclobutanones **4** as a major product instead of cyclopropanes **3**, that are more typically obtained by the reaction of arylthiols with **1a**. In an attempt to rationalize this result, we hypothesized that Brønsted acids might catalyse the reaction, promoting the nucleophile addition, leading to Nu-cyclobutanediol intermediates type-**I** and subsequently to the stabilized cationic intermediate **II**. Depending on the stabilization of this cyclobutylthionium species, this intermediate would evolve into the carbaldehyde **3** or further rearrange to furnish the adduct **4**. Again, aldehydes **3** might be considered as a reaction intermediate and a further protonation might be able to promote a new C3-C4 ring expansion reaction allowing access to α-thiocyclobutanones **4** species. Moreover, choosing the appropriate reaction conditions, we could perform a direct acid-promoted tandem thiol-addition cyclobutanones **4** synthesis from **1a** (scheme 1).

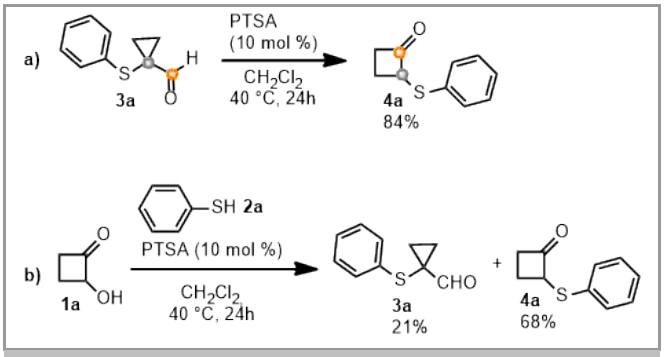


Scheme 1 Brønsted-acid catalysed access to arylthio-derivatives **3** and **4**.

Indeed, access to intermediates **I** and analogous ring contraction reactions have been documented for 2-halocyclobutanones, leading to cyclopropane carboxylic acid derivatives,[2,14] while cyclobutanediols undergo Lewis acid mediated ring contraction to provide cyclopropane carbaldehyde or ketone derivatives.[2,3] However, to the best of our knowledge, there are no examples in the literature of catalytic one-pot reactions capable of providing 2-thio-substituted cyclobutanone adducts from 2-hydroxycyclobutanones.

Results and Discussion

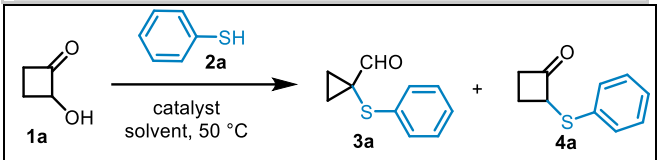
To evaluate our hypothesis and prove the central role of the isolable intermediate **3** in the synthesis of 2-functionalized cyclobutanones, we first investigated the background C3-C4 ring expansion reaction of **3a** into the arylthio-cyclobutanone **4a**. As a first attempt, we carried out the reaction of **3a** with PTSA (10 mol%) in CH_2Cl_2 at 40 °C. We were delighted to find that the desired product **4a** could be isolated from the reaction mixtures in satisfactory yields (84%) after 24 h (scheme 2a). In a second experiment, 2-hydroxycyclobutanone **1a** was reacted with **2a**, in CH_2Cl_2 at 40 °C in presence of PTSA (10 mol%). Even in this case, the cyclobutanone **4a** was isolated from the reaction mixture in acceptable yields (68%) accompanied by 21% of carbaldehyde **3a** (scheme 2b).



Scheme 2 a) Acid catalysed C3-C4 ring expansion of carbaldehyde **3a** to ketone **4a**. b) Direct acid catalysed synthesis of cyclobutanone **4a** from **1a**.

These results prompted us to investigate the two processes. Further insights might, in fact, allow access to 2-substituted cyclobutanones via a tandem methodology, while identifying better performing catalysts and more benign solvents than CH_2Cl_2. Different reaction conditions were screened for the reaction between **1a** and **2a**, with a view to maximize the chemical yield of **4a** (Table 1). Since reactions carried out in neat conditions were not performing, we investigated a panel of solvents including toluene or cyclohexane (entries 2, 3) at 50 °C, which showed no benefit with respect to reactions carried out in dichloromethane (entry 1). However, using 1,4-dioxane gave significantly better yield of **4a** (88%) along with traces amount of compound **3a** after 16 hours (entry 4). A slightly better result was achieved by using THF as a solvent, allowing to isolate compound **4a** in 90% yield (entry 5). A series of Brønsted acids were then evaluated. Methane sulfonic acid (MSA, entry 6) yielded **4a** in acceptable conversions (65%), whereas diphenylphosphate (DPPA) performed less well (20%, entry 7). A moderate yield was obtained using SAC4 sulfonic acid calix(4)arene (62%, entry 8) and CSA (50%, entry 9). Finally, sulfonic resins were screened showing comparable or better results than using PTSA as a catalyst. In particular, Amberlyst-15, Amberlyst-35, and Nafion NR50 provided **4a** in respectively 90, 85 and 93% yield (entries 10-12). Further experiments were performed in order to finely tune the reaction conditions (concentrations, catalyst loading, temperature, see ESI), revealing that the best results could be achieved by using NR50 (10 mol%) in THF at 50 °C, producing **4a** in 94% yield, with aldehyde **3a** not observed (entry 13).

Table 1 Optimisation of reaction conditions to directly access **4a**[a]

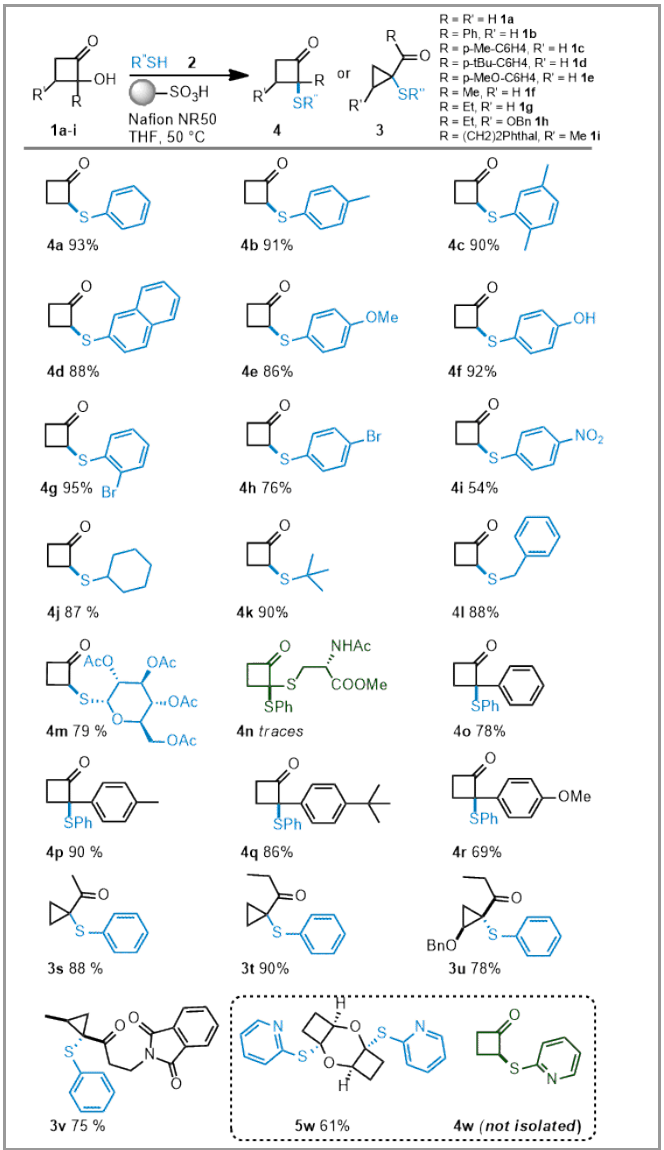


Entry	Catalyst (mol%)	Solvent	Time/h	Yield[b] 4a (3a) /%
1	PTSA (20)	CH_2Cl_2[c]	24	68 (-)
2	PTSA (20)	toluene	24	38 (11)
3	PTSA (20)	cyclohexane	24	31 (10)
4	PTSA (20)	1,4-dioxane	24	88 (-)
5	PTSA (20)	THF	24	90 (-)
6	MSA (20)	THF	24	65 (12)
7	DPPA (20)	THF	24	20 (<5)
8	SAC4 (20)	THF	24	62 (<5)
9	CSA (20)	THF	24	50 (<5)
10	Amberlyst-15 (20)	THF	24	90 (-)
11	Amberlyst-35 (20)	THF	24	85 (-)
12	Nafion NR50 (20)	THF	24	93 (<5)
13	Nafion NR50 (10)	THF[d]	36	94 (-)

[a] Reactions were performed with 0.58 mmol of **1a**, **2a** (1.0 equiv.), catalyst (20-10 mol%), solvent (2.0 mL) at 50 °C, and followed by GC-MS. [b] Isolated yield calculated after flash chromatography purification. [c] Reaction performed at 40 °C. [d] Reaction performed at 60 °C.

With the optimized reaction conditions in hand, we next examined the reaction scope using a series of substituted thiols (Scheme 3). A high substituent tolerance in thiols **2** emerged, allowing access to a good variety of 2-aryl- and 2-alkylthiocyclobutanones **4**. 4-Methylbenzene thiol and 2,5-dimethylbenzene thiol **2b-c**, independently of their substitution pattern, furnished the corresponding adducts **4b-c** in uniformly high yields (91-90%). Similarly, 2-naphthalenethiol **2d** gave **4d** in 88% yield. EDG-substituted 3-methoxy and 4-hydroxy-benzenethiol **2e** and **2f** gave good yields of the corresponding ketones **4e** (86%) and **4f** (92). Moreover, reactions of **1a** with haloarylthiols **2g-h** proceeded efficiently to afford the adducts **4g-h** in good to excellent yields (95% and 76%, respectively). On the other hand, 4-nitrothiophenol **2i** provided **4i** in 54% yield accompanied by 17% of carbaldehyde **3i**. Furthermore, the reaction carried out with alkylthiols **2j-2l** furnished cyclobutanones **5j-l** in respectively 87, 90 and 88 % yields. Optically pure 1-thio-β-D-glucose tetraacetate **2m** and (*S*)-*N*-acyl-cysteine methyl ester **2n** were then reacted with **1a** in the operational conditions described above. 2-Thio-glucose-cyclobutanone **4m** was produced in 79% as a single diastereoisomer, while derivative **4n** was observed in traces along with an inseparable mixture of unidentified products. To

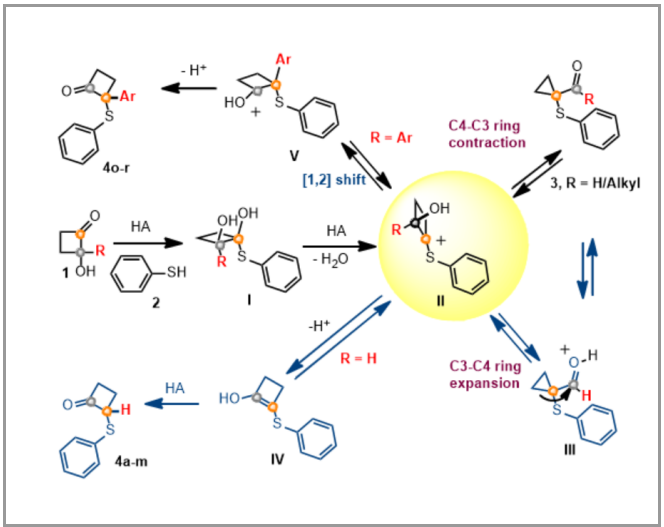
extend the scope of this reaction, 2-alkyl- and 2-arylsubstituted cyclobutanones **1b-h**[1b] were reacted with thiophenol **2a**. 2-Aryl-hydroxycyclobutanones **1b-e** furnished the corresponding 2-aryl-2-sulfanylcyclobutanones **4o-r** in high yields with no traces of the corresponding cyclopropylketone derivatives **3**. 2-alkylketones **1f-i**, on the other hand, produced only the corresponding cyclopropane adducts **3r-u**. Finally, experiments carried out with mercaptopyridine **2w** afforded, as a predominant reaction product, the tricyclic compound **5w** (61% yield), very likely obtained by dimerization of the corresponding cyclobutanone **4w**.[8]



Scheme 3 Substrate scope for the direct access to cyclobutanones **4**. Reactions were performed with 0.58 mmol of **1a-i**, **2a-n**, **2t** (1.0 equiv.), NR50 10 mol %, THF (2.0 mL) at 50 °C, and followed by GC-MS. Isolated yield calculated after flash chromatography purification.

Mechanisms and Quantum Chemical DFT calculations

As described above, both 2-hydroxycyclobutanone (**1a**) and 2-aryl-2-hydroxycyclobutanones (**1b-d**) underwent acid promoted thiol addition, furnishing the corresponding adducts **4**. However, the mechanisms that lead to obtaining these species are not likely to be common to both substrates, and different paths need to be proposed in order to rationalize these results (Scheme 4). Starting from the experimental results, we assumed that protonation of **1a** followed by thiol nucleophilic addition would lead to the formation of a cyclobutane-1,2-diol species **I**[6,7] which, according to our initial hypothesis (Scheme 1), undergoes dehydration furnishing the cyclobutylthionium carbocation **II**. This intermediate can be prone to further C4-C3 ring-contraction leading to the formation of cyclopropylcarbaldehydes **3** or ketones **5**.[7,15] When reactions are carried out at 50-60 °C, compounds **3** can be involved in a rapid acid-catalyzed C3-C4 ring expansion, yielding the corresponding cyclobutanones **4**. On the other hand, the cyclobutylthionium carbocation type-**II** generated by thiol addition to cyclobutanones **1f-i**, seems to be not involved in this process, furnishing the corresponding cyclopropane adducts **3**.[1617] Also, 2-aryl-2-hydroxycyclobutanones **1b-e**, behaved differently from the alkyl adducts **1f-i** when subjected to reaction with thiols under the reaction conditions described above. In fact, we were not able to observe the formation of the corresponding cyclopropane adducts **3** but only ketones **4**. These observations are summarized in scheme 4.

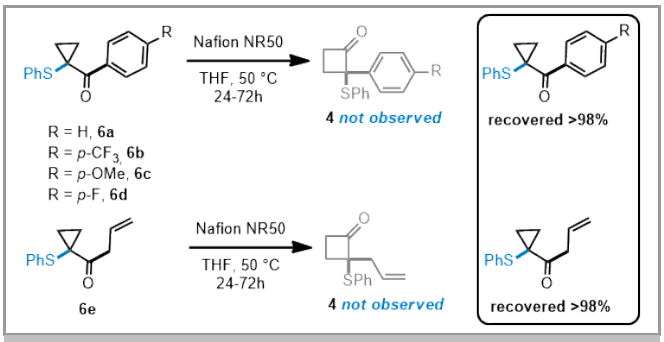


Scheme 4 Rationalisation of the transformation of cyclobutanones **1** into cyclopropyl derivatives **3** or **5** and 2-arylsulfanyl cyclobutanones **4** *via* the intermediacy of cyclobutylthionium cation **II**.

To verify the intervention of a transient **3**-like adducts for these compounds, a series of cyclopropylaryl ketones **6a-d** and **6e** were synthetized[14] (see ESI) and submitted to acid-promoted C3-C4 ring expansion (scheme 5). However, ^{1}H NMR analysis of the crude reaction mixtures did not highlight the formation of the corresponding cyclobutyl adducts **4** and the starting materials were recovered unchanged even after several days stirring at 80 °C.

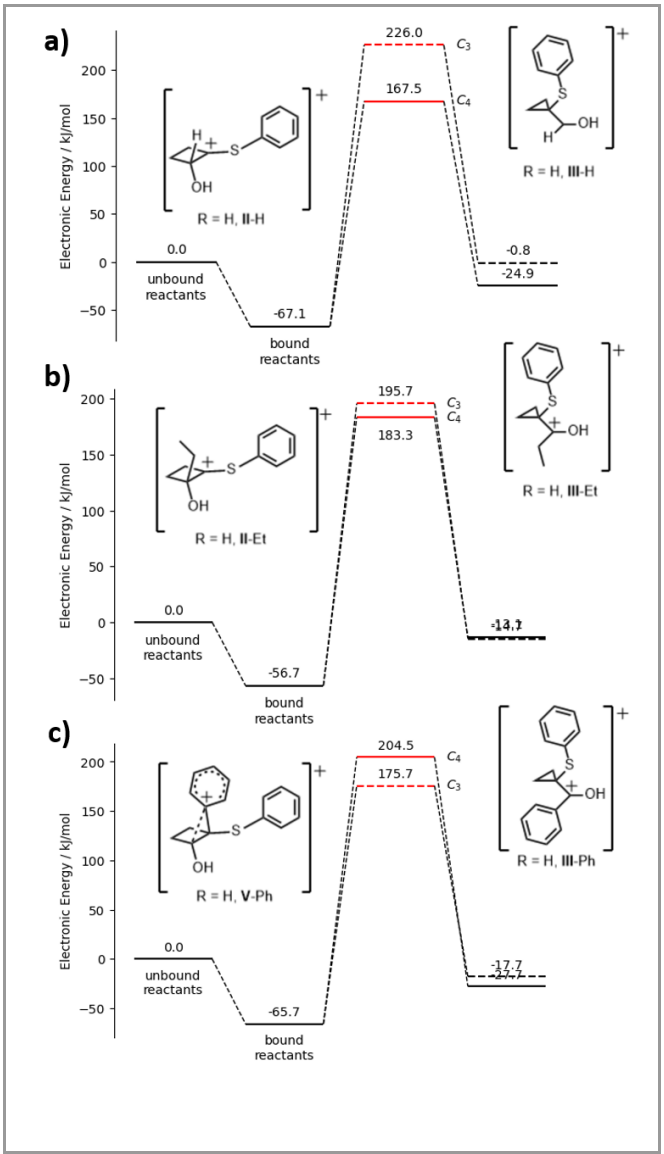
This last observation led us to suppose that the **4o-r** cyclobutanone derivatives reported in scheme 3 were formed by means of a [1,2]-transposition as hypothesized in our previous work and not with the intermediacy of a 3-like cyclopropyl transient species.[7]

With the aim of rationalizing the processes that could be involved in these transformations, we conducted quantum chemical calculations to test the hypothesis of C3-C4 ring contraction or expansion in the carbocation state (Scheme 6).



Scheme 5 Acid catalysed reaction of cyclopropyl ketones **3x-y** towards 2-arylthiocyclobutanones.

Calculations were performed with NWChem[16] 7.0.2 using density functional theory with a Def2-SVP basis set[17], PBE0 functional[18] with dispersion (vdw-3) correction[19] (DFT-D3). The THF solvent was represented via the COSMO solvation model[20] (with dielectric constant εr = 7.43). Density functional theory with a continuum model of solvent has been successfully applied to calculation of aromatic electronic energies,[21] while the DFT-D3 dispersion correction is a new feature in quantum chemistry that is expected to improve the accuracy of electronic structure and energy calculations of carbocations[22]. Scheme 6 shows energy levels (relative to original unbound reactants) of bound reactants (**I**), carbocations (**II**) and products. Total energy levels are calculated by adding the energy of the catalyst PTSA, its corresponding base, water and hydronium alongside the target species as required in order to maintain an identical number of atoms throughout the reaction for the three cases of R=H ($C_{17}H_{20}O_5S_2$), R=Et ($C_{19}H_{24}O_5S_2$), and R=Ph ($C_{23}H_{24}O_5S_2$). Electronic energies (see ESI) confirm the observation that the relative stability of the transition state cyclobutyl and cyclopropyl carbocations switches between alkyl (R=Et) and aryl (R=Ph) substituents. For R=Et (also R=H), the cyclobutyl carbocation is more stable than the cyclopropyl carbocation, while the reverse is true with R=Ph. In order to confirm that this trend is maintained at finite temperature, we performed a frequency analysis computing energy gradients[23] to evaluate the vibrational states of all species. We calculated the corresponding free energy at T=45 °C, adding the enthalpy and entropy of rotational and vibrational states. Free energy diagrams are presented in Scheme 6, following the same trend seen in the electronic energies. While the cyclobutyl carbocation is more stable than cyclopropyl for both R=H and R=Et, the energy difference diminishes with ΔG=44.7 kJ/mol for R=H, falling to ΔG=13.2 kJ/mol for R=Et. For R=Ph the cyclopropyl carbocation is more stable with ΔG=-41.1 kJ/mol. Quantum chemical calculations confirm the dependence of the carbocation energy levels on the R substituent. With R=H the C4 carbocation is more stable than the C3 counterpoint, while with R=Ph the reverse is true. So, excluding the intermediacy of a cyclopropyl-derivative (see scheme 4), we hypothesize that thionium-ion **II** might stabilize its positive charge by sigmatropic 1,2-shift migration of an aromatic group leading to cationic species **V**, that would further evolve in cyclobutanone **4**. Nevertheless, a superior migratory aptitude of the aromatic groups can be evoked in this pinacol-like rearrangement, justifying the fact that alkyl substituted cyclobutanones **1f-i** do not allow access to the corresponding ketones **4**.



Scheme 6 Total electronic energy level diagrams of substrate with PTSA catalyst in THF solvent calculated by density function theory (a) R=H, $C_{17}H_{20}O_5S_2$ (b) R=Et, $C_{19}H_{24}O_5S_2$ (c) R=Ph $C_{23}H_{24}O_5S_2$, (c) R = Ph, $C_{23}H_{24}O_5S_2$. F

1D NMR and Raman investigations on the synthesis of 3b and 4b from cyclobutanone 1a

As a final aspect of this study, the acid-catalyzed addition reaction of 4-methylbenzene thiol **2b** to **1a** and its evolution were followed, until compound **4b** is obtained, by running a series of *in situ* NMR analyses aiming to reveal the intermediacy of cyclopropyl-adducts **3b** and its further conversion into the desired 2-arylthiocyclobutanone **4b** (Figure 1). These experiments were performed by following specific proton signals; the proton at 1.51 ppm for the carbaldehyde **3b**, the

proton signals at 4.96 ppm for the cyclobutanone **1a** (Figure 1) and 4.89 ppm for the ketone **4b** . When reactions between **1a** and thiol **2b** were performed at room temperature, **1a** (black) was quantitatively converted after a few minutes into compound **3b** (red), while **4b** was not observed in the reaction mixture. On the other hand, when cyclobutanone **1a** was reacted with thiol **2b** at 50 °C, we still observed the fast formation of the carbaldehyde **3b** (t_0 > 90% yield, red), but also observed the emergence of a transient species, later identified as the 2-phenylsulfanyl-cyclobut-1-enol **IV** (violet), which slowly decreases as the cyclobutanone **4b** increased (blue). The reaction of **1a** and **2b** was monitored through Raman spectroscopy, observing the decrease/increase of the carbonyl functional groups areas of **1a** (1776 cm^{-1}), **3b** (1581 cm^{-1}) and **4b** (1700 cm^{-1}). These analyses are in excellent agreement with the ^1H NMR measurements as regards the reaction between **1a** and thiol **2b** to obtain carbaldehyde **3b** (fast). The acid-catalyzed conversion of **3b** into the corresponding adduct **4b** is significantly slower and requires more drastic reaction conditions (50° C/24-40h), likely due to the establishment of an equilibrium between the two species **3b** and **4b** due to the increase of water which is produced during the formation of the cyclobutylthionium **II**. Furthermore, the experiments conducted within-situ NMR highlight the fact that the stirring and diffusion of the reactants in the reaction medium play a fundamental role in this process. In fact, reactions performed in NMR tubes show a slower conversion of **3b** to **4b** (Figure 1, b blue), with conversion to **4b** obtained only after 40 hours reaction. On the other hand, in situ Raman analyses, performed by direct exposition of the reaction vial to the Raman source, show faster conversion (24h). In summary, these in situ experiments corroborate our hypothesis reported in the scheme 4 and are also in line with the DFT-calculations.

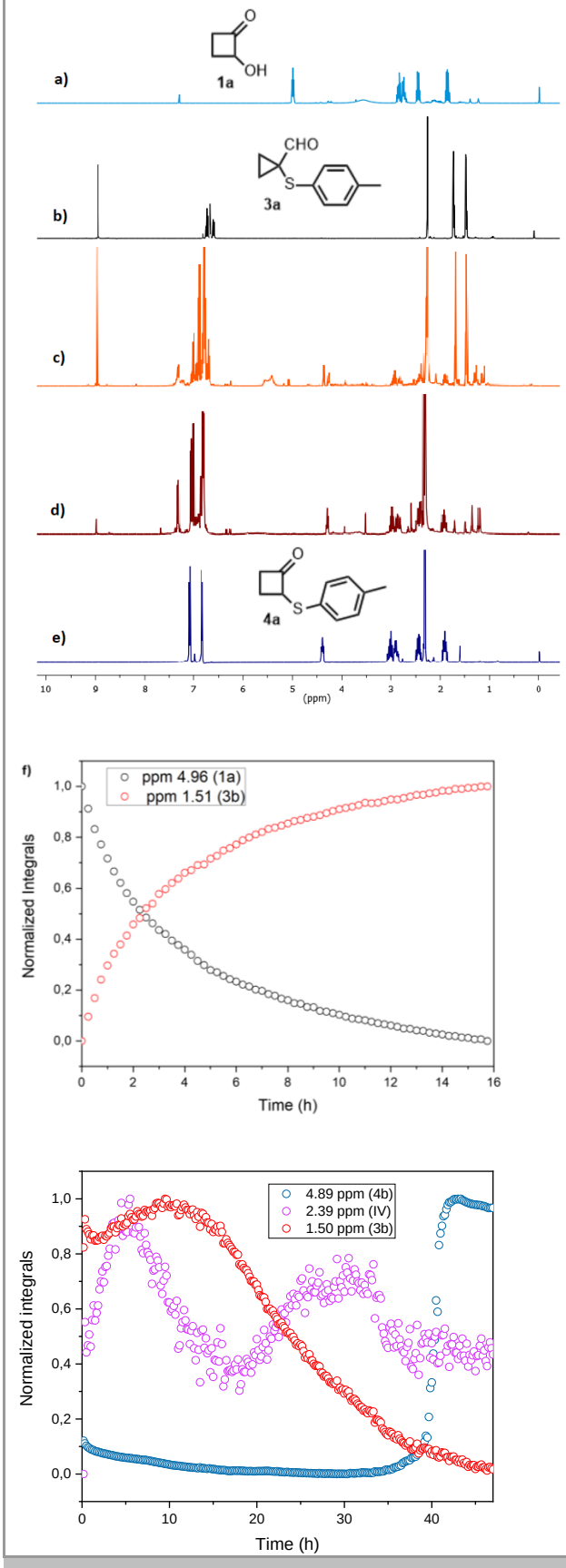


Figure 1 a) 1H NMR spectra of 1a, b) 1H NMR spectra of 3b, c-d) 1H NMR analysis of the reaction between **1a** and **2b** at 50° C; e) 1H NMR spectra of

4b;f) NMR analysis plot of the reaction between **1a** and **2b** at 50 °C.

Together these analyses provide evidence confirming that the cyclobutylthionium cation **II**, generated from the diol **I** through an acid-catalysed tandem thiol-addition, C4-C3-ring contraction, C3-C4-ring expansion sequence, represents a plausible mechanistic model for the production of cyclobutanones **4** from **1a**.[15]

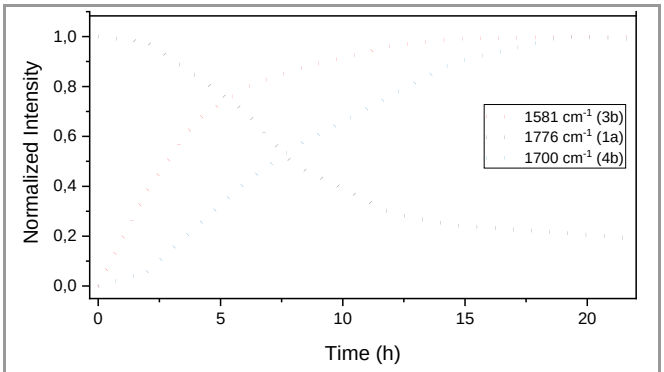


Figure 2 Raman spectra and analysis plot of the reaction between **1a** and **2b** at 50 °C.

Conclusions

In summary, a new Brønsted acid-catalyzed C4-C3 ring contraction reaction, which allows access to arylthiocyclobutanones from 2-hydroxycyclobutanone derivatives, was presented. The transformation is achieved via a cascade metal-free process under mild conditions; substituent electronic effects of the cyclobutanone species proved to play a crucial role in the process. Quantum Chemical-DFT calculations were performed to help rationalize the experimental results. In particular, the migratory attitude of the aromatic group in 2-aryl-2-hydroxy cyclobutanone derivatives was highlighted, indicating the path to the corresponding 2-aryl-2-sulfanyl-cyclobutanones. On the other hand, a justification was provided for to the low migratory aptitude of alkyl groups and the consequent cyclopropyl ketones. Finally, 1D NMR and in situ Raman analyses highlighted how the synthesis of derivatives **4b** proceeds through the formation of cyclopropyl carbaldehyde adducts which, by subsequent acid-catalysed reaction, lead to the formation of the corresponding four-membered ring compounds. All these investigations allowed to better understand and rationalise the described catalytic process. Following from the knowledge acquired, further investigations are ongoing in our laboratories focussing on the asymmetric synthesis of enantiomerically enriched arylthiocyclobutanone derivatives.

Procedures

PTSA, Diphenyl phosphate, SAC4, CSA, Amberlyst 15, Amberlyst 35, NR50 and thiols **2a-n**, **2w** were purchased from Sigma-Aldrich and used without further purification. Cyclobutanones 1b-h were prepared following the procedures reported in the ESI and in our previous works.[1b,7] Unless noted otherwise, all experiments were carried out in a 5 mL vial closed with a screw cap and equipped with a magnetic stirring bar. Analytical thin-layer chromatography was performed using 0.25 mm Aldrich silica gel 60-F plates. Flash chromatography was performed using Merck silica gel (70–200 mesh). Yields refer to chromatographically and spectroscopically pure materials. Melting points were determined with a Büchi M-560 apparatus. Infrared spectra were recorded on FT-IR Bruker Equinox-55 or Thermo Fisher Scientific Nicolet IS50 FTIR spectrophotometers and are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were obtained on Bruker DRX 600 (^1H, 600 MHz; ^{13}C, 150 MHz) or Varian 500 (^1H, 500 MHz; ^{13}C, 126 MHz) spectrometers at 27 °C using $CDCl_3$ (internal reference = 7.26 ppm) as the solvent. ^{13}C NMR were recorded at 126 MHz (internal reference = 77.00 ppm) using $CDCl_3$ as the solvent. Chemical shifts (δ) are given in ppm. Coupling constants (*J*) are reported in Hz. Low-resolution mass spectrometry was performed an Agilent-HP GC-MS (EI, 70 eV). High-resolution mass spectrometry (HRMS) was performed in fast atom bombardment (FAB+) ionization mode (ESI) using Bruker micrOTF-Q II and/or Agilent QTOF 6520 instruments.

General procedure for the synthesis of arylthiol cyclobutanones 4a-r and cyclopropane ketones 3s-v

To a THF (3 mL) solution of **1a** (50 mg, 0.58 mmol), benzenethiol **2a** (64 mg, 0.58 mmol) and NR50 were added. The reaction mixture was warmed to 50 °C and stirred for 24h. The reaction solution was concentrated under reduced pressure and purified by flash chromatography using 9:1 to 5:1 mixture of hexanes/Et_2O.

2-(phenylthio)cyclobutanone (**4a**) Yield: 96 mg (93%); yellow solid. All analytical data were in good accordance with reported data.[13]

2-(*p*-tolylthio)cyclobutanone (**4b**) Yield: 101 mg (91%); yellow solid. All analytical data were in good accordance with reported data.[13]

2-((2,5-dimethylphenyl)thio)cyclobutanone (**4c**) Yield: 107 mg (90%); yellow oil.

FTIR (ν): 3002, 2890, 1790, 1128, 884 cm^{-1}.

^1H NMR (500 MHz): δ = 7.25 (d, J = 11.3 Hz, 1H), 7.07 (d, J = 7.7 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 4-60-4.34 (m, 1H), 3.19-2.99 (m, 1H), 2.64-2.44 (m, 1H), 2.36 (s, 3H), 2.30 (s, 3H), 2.07-1.87 (m, 1H).

^{13}C NMR (126 MHz): δ = 204.8, 136.1, 135.6, 132.7, 131.8, 130.0, 128.0, 59.0, 45.0, 20.8, 20.1, 19.0.

HRMS (ESI): *m/z* $[M\text{-}Na]^+$ calcd for $C_{12}H_{14}NaOS$; found: 229,0670.

2-(naphthalen-2-ylthio)cyclobutanone (**4d**) Yield: 116 mg (88%); yellow solid (M.p. = 64-65°C).

FTIR (ν): 3204, 1790, 1278 cm^{-1}.

^1H NMR (500 MHz): δ = 7.97 (s, 1H), 7.82 (dd, J = 7.8, 5.1 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.54 (dd, J = 8.5, 1.8 Hz, 1H), 7.50 (ddd, J = 9.5, 5.6, 3.4 Hz, 2H), 4.61 (dt, J = 9.8, 7.1, 2.7 Hz 1H), 3.13 (dddd, J = 18.0, 10.3, 7.8, 2.7 Hz, 1H), 3.08-2.98 (m, 1H), 2.77-2.45 (m, 1H), 2.16-1.91 (m, 1H).

^{13}C NMR (126 MHz): δ = 203.4, 133.4, 133.2, 131.8, 128.7, 127.7, 127.0, 126.7, 126.2, 126.0, 59.8, 44.9, 18.5

HRMS (ESI): *m/z* $[M\text{-}Na]^+$ calcd for $C_{14}H_{12}NaOS$; found: 251,2995.

2-((4-methoxyphenyl)thio)cyclobutanone (**4e**) Yield: 116 mg (96%); yellow oil. All analytical data were in good accordance with reported data.[13,15a]

2-((4-hydroxyphenyl)thio)cyclobutanone (**4f**) Yield: 103 mg (92%); yellow oil.

FTIR (ν): 3320, 3004, 2948, 1792, 1490, 1289 cm^{-1}.

^{1}H NMR (500 MHz): δ = 7.38 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.6 Hz, 2H), 6.14 (s, 1H), 4.49-4.20 (m, 1H), 3.00 (dddd, J = 17.9, 10.4, 7.5, 2.9 Hz, 1H), 2.91-2.70 (m, 1H), 2.58-2.29 (m, 1H), 1.93 (ddt, J = 11.8, 10.5, 7.3 Hz, 1H).

^{13}C NMR (126 MHz): δ = 207.3, 156.5, 136.3, 132.1, 116.1, 60.6, 44.8, 18.1.

HRMS (ESI): *m/z* [M-Na]$^+$ calcd for $C_{10}H_{10}NaO_2S$; 217,0301.

2-((2-bromophenyl)thio)cyclobutanone (**4g**) Yield: 141 mg (95%); yellow oil.

FTIR (ν): 3012, 2994, 1790, 1490, 1291, 890 cm^{-1}.

^{1}H NMR (500 MHz): δ = 7.55 (dd, J 0 8.0, 1.2 Hz, 1H), 7.49 (dd, J = 7.9, 1.4 Hz, 1H), 7.30-7.27 (m, 1H), 7.11-7.06 (m, 1H), 4.64 (ddt, J = 9.4, 6.6, 2.5 Hz, 1H), 3.30-3.11 (m, 2H), 2.59 (dtd, J = 12.0, 9.8, 6.4 Hz, 1H), 2.03 (dddd, J = 12.1, 7.5, 6.8 Hz, 1H).

^{13}C NMR (126 MHz): δ = 203.8, 136.0, 132.9, 130.3, 127.9, 127.7, 123.7, 58.0, 45.3, 18.5.

HRMS (ESI): *m/z* [M-Na]$^+$ calcd for $C_{10}H_9BrNaOS$; found: 278,9455.

2-((4-bromophenyl)thio)cyclobutanone (**4h**) Yield: 113 mg (76%); yellow solid. All analytical data were in good accordance with reported data.[13]

2-((4-nitrophenyl)thio)cyclobutanone (**4i**) Yield: 70 mg (54%); yellow solid. All analytical data were in good accordance with reported data.[7]

2-(cyclohexylthio)cyclobutanone (**4j**) Yield: 93 mg (87%); yellow solid. All analytical data were in good accordance with reported data.[7]

2-(*tert*-butylthio)cyclobutanone (**4k**) Yield: 82 mg (90%); yellow solid. All analytical data were in good accordance with reported data.[7]

2-(benzylthio)cyclobutanone (**4l**) Yield: 98 mg (88%); yellow solid. All analytical data were in good accordance with reported data.[13]

5-(acetoxymethyl)-6-((2-oxocyclobutyl)thio)tetrahydro-2H-pyran-2,3,4-triyl triacetate (**4m**) Yield: 198 mg (79%); colourless oil, $[a]_D^{25}$ = -24 (*c* = 1.0 $CHCl_3$)

FTIR (ν): 2924, 2850, 1713, 1788 cm^{-1}.

^{1}H NMR (500 MHz): δ = 5.12 (t, J = 9.4 Hz, 1H), 5.04 (t, J = 9.7 Hz, 1H), 4.90 (t, J = 9.6 Hz, 2H), 4.48 (t, J = 9.8 Hz, 1H), 4.18 (dd, J = 12.5, 4.8 Hz, 1H), 4.06 (d, J = 11.7 Hz, 1H), 3.66 (dd, J = 10.0, 2.6 Hz, 1H), 2.84 – 2.72 (m, 1H), 2.72 – 2.60 (m, 1H), 2.39 (ddd, J = 14.2, 10.5, 4.2 Hz, 1H), 2.24 (d, J = 9.9 Hz, 1H), 2.03 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.94 (s, 3H), 1.83 – 1.70 (m, 1H).

^{13}C NMR (126 MHz): δ = 203.2, 170.6, 170.1, 169.6, 169.3, 78.7, 76.3, 73.5, 68.1, 62.0, 39.0, 21.7, 20.64.

HRMS (ESI): *m/z* [M-Na]$^+$ calcd for $C_{18}H_{24}NaO_{10}S$; found: 455,0989.

2-phenyl-2-(phenylthio)cyclobutanone (**4o**) Yield: 115 mg (78%); yellow oil. All analytical data were in good accordance with reported data.[7]

2-(phenylthio)-2-(*p*-tolyl)cyclobutanone (**4p**) Yield: 139 mg (90%); yellow oil.

FTIR (ν): 3005, 2980, 1790, 1290 cm^{-1}.

^{1}H NMR (500 MHz): δ = 7.20 – 7.13 (m, 5H), 7.10 (d, J = 8.1 Hz, 2H), 6.99 (d, J = 7.9 Hz, 2H), 3.11 (dd, J = 10.4, 7.5 Hz, 1H), 3.01 – 2.80 (m, 1H), 2.66 – 2.43 (m, 1H), 2.47 – 2.28 (m, 1H), 2.24 (s, 3H).

^{13}C NMR (126 MHz): δ = 204.4, 137.3, 136.2, 129.2, 129.0, 128.5, 127.5, 127.1, 72.6, 42.9, 25.8, 21.1.

HRMS (ESI): *m/z* [M-Na]$^+$ $C_{17}H_{16}NaOS$; found: 291,0825.

2-(4-(*tert*-butyl)phenyl)-2-(phenylthio)cyclobutanone (**4q**) Yield: 154 mg (86%); colorless oil.

FTIR (ν): 3012, 2989, 1784, 1278 cm^{-1}.

^{1}H NMR (500 MHz): δ = 7.68-7.60 (m, 1H), 7.54-7.46 (m, 2H), 7.38-7.20 (m, 6H), 3.14 (ddd, J = 17.9, 10.4, 7.5 Hz, 1H), 3.00-2.91 (m, 1H), 2.70-2.59 (m, 1H), 2.49-2.39 (m, 1H 1.30 (s, 9H).

^{13}C NMR (126 MHz): δ = 204.6, 150.7, 136.2, 134.8, 131.3, 129.3, 128.5, 126.9, 125.9, 42.9, 34.5, 31.2, 25.6.

HRMS (ESI): *m/z* [M-Na]$^+$ calcd for $C_{20}H_{22}NaOS$; found: 333,1289.

2-(4-methoxyphenyl)-2-(phenylthio)cyclobutanone (**4r**) Yield: 114 mg (69%); yellow oil.

FTIR (ν): 3010, 2991, 1788, 1280 cm^{-1}.

^{1}H NMR (500 MHz): δ = 8.13-8.08 (m, 2H), 7.50-7.38 (m, 3H), 7.01-6.82 (m, 5H), 3.79 (s, 3H), 3.01 – 2.80 (m, 1H), 2.90 (q, J = 7.3 Hz, 1H), 2.53 (q, J = 7.1 Hz, 1H), 2.43 (q, J = 7.2 Hz, 2H).

^{13}C NMR (126 MHz): δ = 204.8, 137.6, 136.2, 129.8, 129.2, 128.4, 127.7, 127.0, 73.4, 42.8, 26.6, 23.4.

HRMS (ESI): *m/z* [M-Na]$^+$ calcd for $C_{17}H_{16}NaO_2S$; found: 307,0774.

1-(1-(phenylthio)cyclopropyl)ethanone (**3s**) Yield: 98 mg (88%); yellow solid. All analytical data were in good accordance with reported data.[7]

1-(1-(phenylthio)cyclopropyl)propan-1-one (**3t**) Yield: 107 mg (90%); yellow solid. All analytical data were in good accordance with reported data.[7]

1-(2-(benzyloxy)-1-(phenylthio)cyclopropyl)propan-1-one (**3u**) Yield: 141 mg (78%); yellow solid. All analytical data were in good accordance with reported data.[7]

2-(3-(2-methyl-1-(phenylthio)cyclopropyl)-3-oxopropyl)isoindoline-1,3-dione (**3v**) Yield: 158 mg (75%); yellow oil.

FTIR (ν): 2994, 1745, 1650, 1512, 1294 cm^{-1}.

^{1}H NMR (500 MHz): δ = 7.72 (dt, J = 8.5, 4.2 Hz, 2H), 7.66 – 7.57 (m, 2H), 7.19 – 7.11 (m, 2H), 7.10 – 7.05 (m, 2H), 7.02 (dd, J = 12.9, 5.5 Hz, 1H), 3.83 (t, J = 7.2 Hz, 2H), 3.30 – 3.17 (m, 2H), 2.12 – 1.99 (m, 1H), 1.90 (dd, J = 9.1, 3.8 Hz, 1H), 1.23 (d, J = 6.2 Hz, 3H), 1.04 (d, J = 6.3 Hz, 1H), 0.91 (dd, J = 7.6, 3.9 Hz, 1H).

^{13}C NMR (126 MHz): δ = 207.8, 168.0, 136.8, 133.8, 132.0, 129.1, 125.3, 123.1, 38.7, 38.5, 33.7, 29.1, 28.2, 14.3.

HRMS (ESI): *m/z* [M-Na]$^+$ calcd for $C_{21}H_{19}NNaO_3S$; found: 388,0988.

General procedure for the synthesis of arylthiol cyclopropanones 3ao, 3ap, 3ar, 3ax

To a -20 °C THF (20 mL) solution of cyclopropyl(phenyl)sulfane (500 mg, 3.3 mmol), *n*-butyllithium (1.6 M in hexane, 2.29 mL) was added dropwise and stirred for 2h. The reaction mixture was cooled to -78 °C and a THF solution of ethyl benzoate (544 mg, 3.6 mmol in 5 mL of THF) was added over 15 minutes and stirred overnight. The reaction mixture was diluted with Et_2O and quenched with a saturated solution of NH_4Cl (10 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography using a 9:1 mixture of hexanes/Et_2O.

phenyl(1-(phenylthio)cyclopropyl)methanone (**6a**) Yield: 536 mg (64%); White solid (M.p. = 70-71°C).[14]

HRMS (ESI): *m/z* [M-Na]$^+$ calcd for $C_{16}H_{14}NaOS$; found: 277,0669.

(1-(phenylthio)cyclopropyl)(4-(trifluoromethyl)phenyl)methanone (6b) Yield: 743 mg (70%); yellow oil.

FTIR (ν): 3002, 2990, 1750, 1298 cm^{-1}.

^{1}H NMR (600 MHz): δ = 7.96 (t, J = 6.7 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H), 7.23-6.97 (m, 5H), 1.74 (d, J = 4.6 Hz, 2H), 1.39 (q, J = 4.6 Hz, 2H).

^{13}C NMR (150 MHz): δ = 197.5, 135.6, 132.9, 129.4, 129.0, 127.8, 126.3, 125.1 (q, J = 3.8Hz), 52.0, 31.3, 17.6.

HRMS (ESI): *m/z* [M-Na]$^+$ calcd for $C_{17}H_{13}F_3NaOS$; found: 345,0541.

(4-methoxyphenyl)(1-(phenylthio)cyclopropyl)methanone (**6c**) Yield: 543 mg (58%); colorless oil.

FTIR (ν): 3040, 2978, 1670, 1480, 1435, 1285, 1255, 990cm^{-1}.

^{1}H NMR (600 MHz): δ = 7.95 (d, J = 8.9 Hz, 2H), 7.28-7.11 (m, 2H), 7.10-6.99 (m, 1H), 6.84 (d, 8.8Hz, 2H), 3.78 (s, 3H), 1.68 (d, J = 2.4 Hz, 2H), 1.29 (d, J = 2.4Hz, 2H).

^{13}C NMR (150 MHz): δ = 196.9, 163.2, 136.3, 131.8, 131.5, 128.9, 128.8, 128.0, 127.7, 125.5, 113.3, 55.4, 30.8, 16.6.

HRMS (ESI): *m/z* [M-Na]$^+$ calcd for $C_{17}H_{16}NaO_2S$; found: 307,0773.

(4-fluorophenyl)(1-(phenylthio)cyclopropyl)methanone (**6d**) Yield: 673 mg (75%); yellow oil.

FTIR (ν): 3007, 2984, 1750, 1294 cm^{-1}.

^{1}H NMR (600 MHz): δ = 7.98-7.91 (m, 2H), 7.22-7.12 (m, 4H), 7.11-7.05 (m, 1H), 7.04-6.98 (m, 2H), 1.68 (q, J0 4.6Hz, 2H), 1.33 (q, J = 4.6Hz, 2H).

^{13}C NMR (150 MHz): δ = 196.3, 165.3 (d, J = 254.3 Hz), 135.8, 132.4 (d, J = 9.2 Hz), 132.0 (d, J = 9.2Hz), 128.9, 127.8, 126.1, 115.2 (d, J = 21.9 Hz), 31.2, 17.0 (two cyclopropyl carbons),

HRMS (ESI): *m/z* [M-Na]$^+$ calcd for $C_{16}H_{13}FNaOS$; found: 295,0569.

1-(1-(phenylthio)cyclopropyl)but-3-en-1-one (**6e**) Yield: 539 mg (75%); yellow oil.

FTIR (ν): 2998, 2984, 1756, 1289 cm^{-1}.

^{1}H NMR (600 MHz): δ = 7.23-7.20 (m, 2H), 7.16-7.12 (m, 2H), 7.10-7.07 (m, 1H), 5.84 (ddt, J = 17.1, 10.3, 6.8 Hz, 1H), 5.05 (ddd, J = 10.3, 2.8, 1.3 Hz, 1H), 4.96 (dq, J = 17.2, 1.5 Hz, 1H), 3.60 (dt, J = 6.8, 1.4 Hz, 1H), 1.77 (q, J = 6.8, 1.4 Hz, 2H), 1.25 (q, J = 4.0 Hz, 2H).

^{13}C NMR (150 MHz): δ = 207.8, 136.9, 131.0, 129.1, 125.9, 125.5, 118.3, 44.6, 32.3, 22.3.

HRMS (ESI): *m/z* [M-Na]$^+$ calcd for $C_{13}H_{14}NaOS$; found: 241,0665.

1,6-bis(pyridin-2-ylthio)-2,7-dioxatricyclo[6.2.0.03,6]decane (**5w**) Yield: 127 mg (61%); yellow oil.

FTIR (ν): 3420, 3053, 3026, 1598, 1480, 1110 cm^{-1}.

^{1}H NMR (500 MHz): δ = 8.40 (d, J = 5.0 Hz, 1H), 8.34 (d, J = 4.2 Hz, 1H), 7.59 – 7.51 (m, 3H), 7.45 – 7.33 (m, 1H), 7.11 (d, J = 8.1 Hz, 1H), 7.07 – 7.01 (m, 2H), 6.94 – 6.86 (m, 1H), 3.66 (t, J = 6.2 Hz, 2H), 3.17 – 3.06 (m, 2H), 1.84 – 1.70 (m, 4H), 1.66 (tt, J = 13.2, 6.7 Hz, 4H).

^{13}C NMR (126 MHz): δ = 159.1, 158.9, 149.5, 149.2, 137.4, 135.9, 122.4, 121.1, 119.7, 119.2, 62.0, 31.1, 29.0, 26.0.

HRMS (ESI): *m/z* [M-Na]$^+$ calcd for $C_{18}H_{18}N_2O_2S_2$; found: 358,0810.

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Supporting Information

YES

Primary Data

NO.

Conflict of Interest

There is no conflict of interest regarding this paper.

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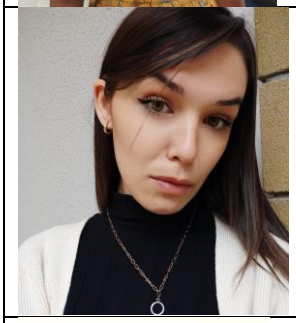
Biosketches

	Stefania Porcu received her PhD degree in Physics from the University of Cagliari working in the materials science and optical spectroscopy research group under the supervision of Professor Pier Carlo Ricci. In 2019 she moved to the College of Engineering (University of Notre Dame, Indiana - USA) supervised by Professor Svetlana Neretina and afterwards, she joined the Professor Radim Beranek research group (Institute of Electrochemistry, University of Ulm - Germany). From January 2021 to May 2021 she worked as research fellow in the physic department of the University of Cagliari within the project CUBER for the study of electrolytes for copper cells in batteries. Since 31st of December 2021 she works at the Physics department of as tenure trach researcher.
	Maria Chiara Cabua obtained her M.Sc. degree in medicinal chemistry from the University of Cagliari in 2019 working on the enantioselective deprotonation and trapping of oxiranes . After a one year spent in the pharmacy sector, she started in 2020 her PhD studies in chemistry whit professor Francesco Secci working on the development of new ecofriendly synthetic methodologies using bio-based sources.
	Viktoria Velichko graduated in 2018 in Pharmacy from Samara State Medical University (Russia) and spent her final exchange semester at CSIC (The State Agency Spanish National Research Council (Consejo Superior de Investigaciones Científicas, CSIC) working on the development of new methods for purification of immunoglobulins. After graduation, she spent a year working in the pharmaceutical industry. In 2020, Viktoria started her PhD at the University of Cagliari, focusing on developing new catalytic batch/continuous flow photoinduced cascade reactions under the supervision of Prof. F. Secci.
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	Francesco Secci was born in 1977. He received his Ph.D. degree in 2006 from the University of Cagliari and Université Paris-Sud (Orsay-France) under the supervision of Prof. P. P. Piras and Dr. J. Ollivier. After a postdoctoral stay (2007-2010) at the University of York, UK (Prof. P. O'Brien) he moved back to Cagliari to start his own research granted by FIRB. From 2013 He served as lecturer at the same university and in 2019, he was promoted to Associate Professor. His research interests are focused on the development of new synthetic methodologies involving strained carbo- and heterocyclic compounds, the study of novel catalytic transformations and their synthetic applications.