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Acid-catalyzed synthesis of functionalized arylthio cyclopropane carbaldehydes and ketones†

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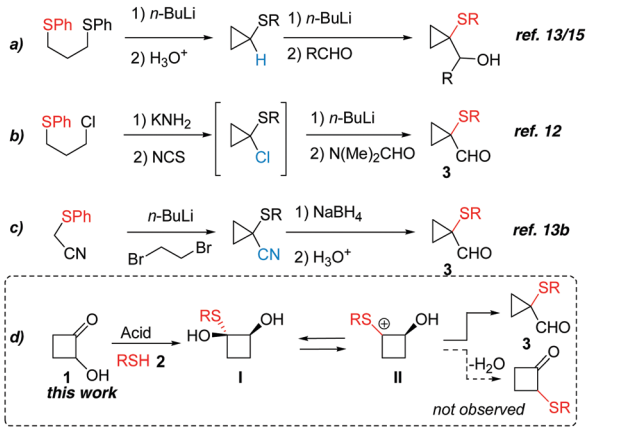
A general strategy for the synthesis of arylthio cyclopropyl carbaldehydes and ketones *via* a Brønsted acid catalyzed arylthiol addition/ring contraction reaction sequence has been exploited. The procedure led to a wide panel of cyclopropyl carbaldehydes in generally high yields and with broad substrate scope. Mechanistic aspects and synthetic applications of this procedure were investigated.

Due to the ease of its preparation[1] and its extensive chemical reactivity[2] 2-hydroxycyclobutanone **1a** constitutes a powerful building block for organic synthesis. Recent applications in ring cleavage reactions,[3] Wittig reaction acetalization,[4] preparation of methylenecyclobutane nucleoside analogues,[5] synthesis of functionalized tryptamines or dioxins,[6] stereoselective aldol reactions[7] and catalytic α-amination reactions underline the synthetic value of this molecule.[8,9] Recently, we initiated studies on the preparation and reactivity of a related series of compounds, 2-(arylthio)-cyclobutanones.[10] Their synthesis was achieved through the organocatalyzed α-sulfanylation of cyclobutanone using diaryl disulfides.[10a] Given the reactivity of **1a** with other nucleophiles, it might appear plausible that it could serve as a convenient precursor for 2-(arylthio)cyclobutanones through substitution reactions with arylthiols **2**. However, we hypothesized that the reaction between **1a** and **2** in the presence of a Brønsted acid would result in the formation of a phenylsulfanyl-cyclobutanediol intermediate **I** and therefrom the sulfur-stabilized cationic intermediate **II**, which would evolve by ring contraction to furnish cyclopropyl carbaldehydes **3** (Scheme 1d). Indeed, analogous ring contraction reactions have been documented for 2-halocyclobutanones, leading to cyclopropane carboxylic acid derivatives,[11] while cyclobutanediols undergo Lewis acid induced ring contraction to provide cyclopropane carbaldehyde or ketone derivatives.[12]

The synthesis of arylthiocyclopropyl carbaldehydes or carbinols, however, is limited mainly to stoichiometric metalation of arylthio ethers followed by trapping with formamides or aldehydes (Scheme 1(a and b))[13–15] or to hydrolysis of cyclopropane carbonitriles (path c).[13b] To evaluate our hypothesis we first examined the reaction between 2-hydroxycyclobutanone **1a** and benzenethiol **2a**, conducted under neat conditions at room temperature for 24 hours using 20 mol% of PTSA as the catalyst. We were delighted to find that the desired product **3a** could be isolated from the reaction mixture in 48% yield, accompanied by a secondary product (10% yield), identified as the cyclopropanol thioketal **4a** (Table 1, entry 1). The use of a panel of solvents toluene, *n*-hexane, EtOAc and THF had a deleterious effect (entries 2, 4–6), so it was gratifying to observe a significantly higher yield of **3a** (93%), along with traces amount of compound **4a**, after only 2 hours reaction time when the reaction was performed in CH_2Cl_2 (entry 3). A series



Scheme 1 Rational design for the acid-catalyzed synthesis of arylthio cyclopropyl derivatives.

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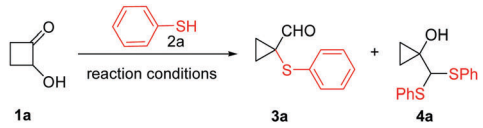
Table 1 Solvent and catalyst studies[a,b]



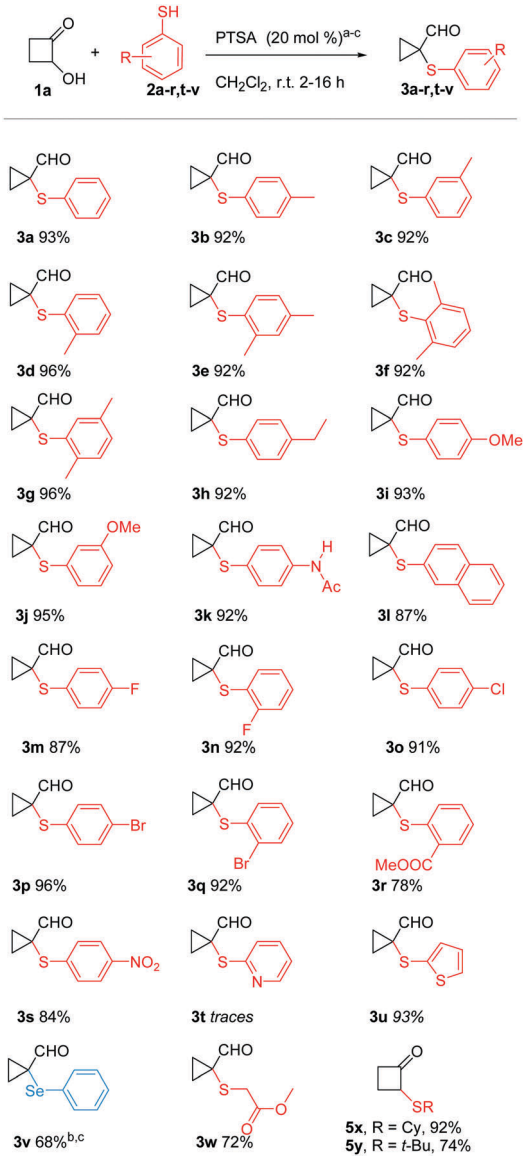
1a 3a 4a

Entry	Catalyst (%)	Solvent	Time (h)	3a, (4a) yields (%)
1	PTSA (20)	—	24	48 (10)
2	PTSA (20)	Toluene	24	36 (—)
3	PTSA (20)	CH_2Cl_2	2	93 (<5)
4	PTSA (20)	Hexane	24	10 (8)
5	PTSA (20)	EtOAc	24	12 (—)
6	PTSA (20)	THF	24	36 (—)[c]
7	H_2SO_4 (20)	CH_2Cl_2	24	68 (10)
8	MSA (20)	CH_2Cl_2	24	66 (5)
9	CSA (20)	CH_2Cl_2	24	49 (—)
10	TFA (20)	CH_2Cl_2	24	23 (—)
11	BF_3–OEt_2 (20)	CH_2Cl_2	24	— (—)
12	PTSA (10)	CH_2Cl_2	12	72 (<5)[c]
13	PTSA (30)	CH_2Cl_2	2	85 (11)

[a] Reactions were performed with 0.58 mmol of **1a**, **2a** (1.0 equiv.), catalyst (10–30 mol%), solvent (2.0 mL) at room temperature, and followed by GC-MS. [b] Isolated yield after flash chromatography. [c] Entries 6 and 12 where repeated in the presence of molecular sieves (3 Å) without yields or selectivity improvement.

of Brønsted acid catalysts were evaluated in $CH_2Cl_2{\cdot}H_2SO_4$ (entry 7) gave the phenylthiocyclopropyl carbaldehyde in acceptable yield (68%), whereas MSA, CSA, and TFA performed less well (entries 8–10). BF_3–OEt_2 was ineffective (entry 11).

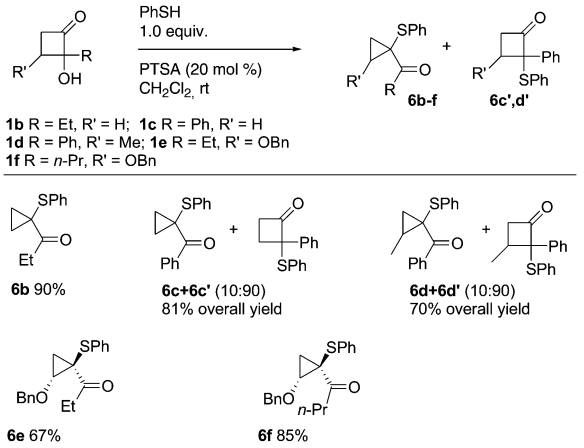
Catalyst loading was also evaluated (entries 12 and 13) showing that the optimum yield of **3a** was afforded using 20 mol% of PTSA. With these optimized reaction conditions in hand, we next examined the reaction scope using a series of substituted arylthiols (Scheme 2). A high substituent tolerance in arylthiols **2** emerged, allowing access to a good variety of functionalized carbaldehydes **3**. Methyl-substituted arylthiols **2b–g**, independently of their substitution pattern, furnished the corresponding adducts **3b–g** in uniformly high yields (92–96%). Similarly, carbaldehyde **3h** was isolated in 92% yield. EDG-substituted *p*-, *m*-methoxyarylthiols **2i–j** and *p*-*N*-acylaminoarylthiol **2k** gave good conversions and yields of the corresponding compounds **3i–k**. The reaction with the more bulky 2-naphthylthiol **2l** as the substrate afforded carbaldehyde **3l** in 87% yield. Reactions of **1a** with haloarylthiols **2m–n** (*p*-, *o*-F), **2o** (*p*-Cl), **2p** (*p*-Br) and **2q** (*o*-Br) all proceeded efficiently to afford the adducts **3m–q** in excellent yields. The acid catalyzed ring-contraction of **1a** worked well even with the EWG-substituted arylthiols **2r** and **2s** which provided **3r** and **3s** in 78% and 84% yields, respectively. Unsatisfactory results were achieved with 2-pyridylthiol **2t** and the carbaldehyde **3t** was only observed in trace amounts by ^{1}H NMR analysis of its crude reaction mixture. Nevertheless, 2-thiophenethiol **2u** was efficiently converted into the corresponding adduct **3u** in 93% yield. In order to evaluate further extensions of this procedure, benzeneselenol **2v** and some alkylthiols (**2w–y**) were tested. Reaction of **1a** with **2v** proceeded smoothly yielding the selenyl-adduct **3v** in 68% yield after 4 hours reaction. Moreover, methyl thioglycolate **2w**, afforded **3w** in 72% yield. On the other hand, reaction carried out with **2x** and **2y**, gave poor yields of the corresponding



Scheme 2 Substrate scope exploration. [a] Reactions were performed with 0.58 mmol of **1a**, **2a–r**, **2t–v** (1.0 equiv.), PTSA 20 mol%, CH_2Cl_2 (2.0 mL) at room temperature and followed by GC-MS. [b] Reaction was carried-out with 0.58 mmol of **1a**, benzene selenol **2s** (1.0 equiv.), PTSA 20 mol%, CH_2Cl_2 (2.0 mL). [c] Diphenyldiselenide was isolated in 22% yield after chromatography.

cyclopropyl carbaldehydes **3x** and **3y**; the predominant reaction products were identified as the cyclobutanones **5x–y**.[16] To test the ring contraction protocol for the synthesis of arylthiocyclopropyl ketones, functionalized 2-hydroxycyclobutanone derivatives **1b–e**[17] were treated with thiophenol **2a** in the presence of PTSA at room temperature. Pleasingly, as shown in Scheme 3, ketone **6b** was isolated in 90% yield after 8 hours reaction time.

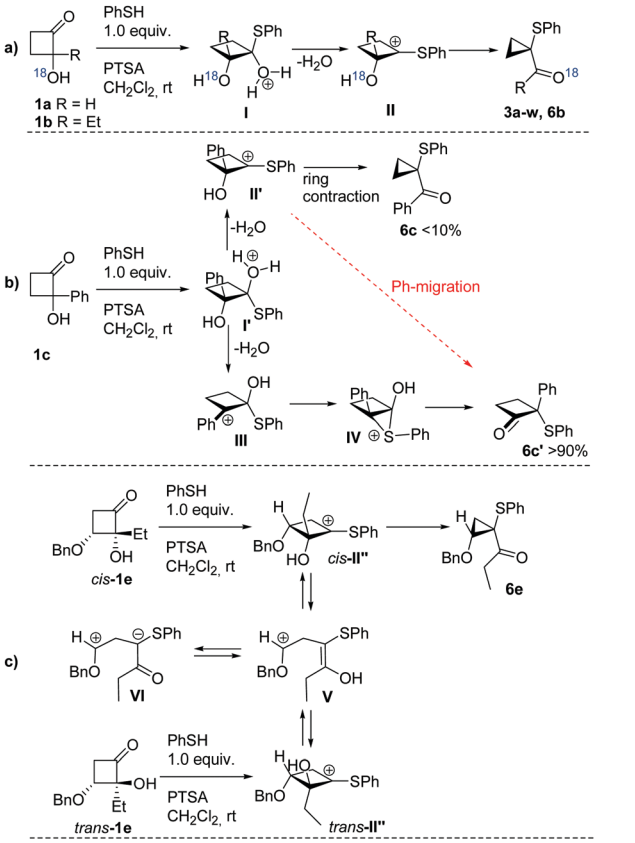
On the other hand, **1c**, bearing a 2-phenyl group, afforded the corresponding cyclopropane **6c** as a 10 : 90 mixture with the cyclobutanone **6c′** in a 81% overall yield. A similar result was achieved when 2-hydroxy-3-methyl-2-phenyl-cyclobutanone **1d** (50 : 50 *cis*/*trans*) was submitted to acid-catalyzed ring-contraction



Scheme 3 Acid catalyzed formal thiophenol-addition–ring contraction of 2-hydroxycyclobutanones **1b–1f**.

in the presence of thiophenol leading to a 10 : 90 mixture of the corresponding compounds **6d** and **6d′** (70% yield). Finally, with the aim to investigate the stereochemical tendency of this reaction, 3-benzyloxy-2-ethyl-2-hydroxy-cyclobutanone *cis*-**1e** and *trans*-**1e** were submitted to reaction with **2a**. Interestingly, both cyclobutanones allowed to isolate in appreciable yields the compound *trans*-**6e** as a single diastereoisomer. Analog results were achieved when 3-benzyloxy-2-hydroxy-2-propyl-cyclobutanone **1f** was treated under the same operational conditions (Scheme 3). Based on the above results, a plausible mechanism for the acid-catalyzed ring-contraction is proposed in Scheme 4. As described on Scheme 1d, protonation of **1a** followed by nucleophilic addition of **2a** leads to the formation of the intermediate cyclobutane-1,2-diol-species **I**.[11d,12]

Further loss of water would give the aryl cyclobutylthionium carbocation **II**. Ring contraction of this intermediate leads to the obtainment of carbaldehydes **3** and cyclopropyl ketone **6b** (Scheme 4, path a). This mechanism has been also investigated using ^{18}O-**1a** allowing to isolate ^{18}O-**3a** in 92% yield (^{18}O-incorporation 78%).[18] Moreover, cyclobutanones bearing a phenyl group on the 2-position, might generate two possible carbocation species (Scheme 4, path b); The first one having a positive charge stabilized by the sulfanyl-group (thionium-ion) **II′** would preferentially lead to the formation of the compound **6c**. On the other hand, the protonation of the hydroxy-group and the loss of a molecule of water from the position-2, would generate a benzylic carbocation **III** which would undergo phenylthio [1,2]-shift through the intermediacy of an episulfonium ion **IV** and leading to the prevalent formation of the 2-phenyl-2-phenylsulfanyl-cyclobutanone **6c′**. Analog result might be achieved by phenyl [1,2]-shift from the adduct **II′**.[19] Finally (Scheme 4, path c), 3-benzyloxycyclobutanones **1e** once reacted with **2a** can be involved in the formation of zwitterionic-like species **VI**[20] by Brønsted acid intermediacy and promoting a ring-opening ring-closing donor–acceptor cyclobutane-rearrangement. This reactivity has been evoked to justify the stereochemical outcome of this reaction. In fact, both pure *cis*- and *trans*-**1e** independently by their stereochemistry, provided exclusively the corresponding

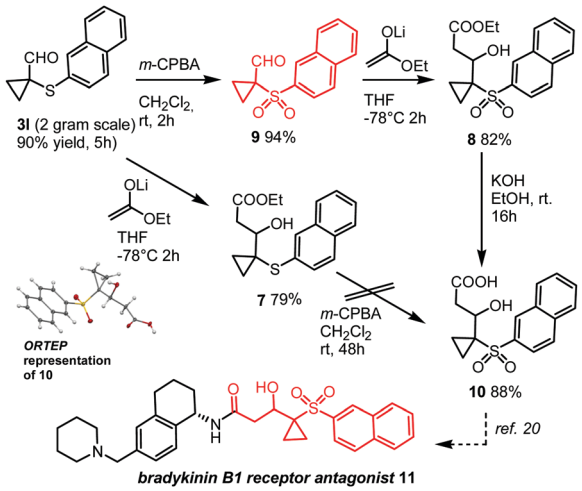


Scheme 4 Proposed mechanism for the synthesis of compounds **3a–w**, **6b**, **6c** and **6e** (see also ESI†).

trans-cyclopropane **6e** in good yields (superimposable results were obtained by using the cyclobutanone **1f**).[21]

In an application of this methodology, we carried out the gram scale preparation of cyclopropylcarbaldehyde **3l**, now obtained in 90% yield, which was used as the starting material for the formal synthesis of the B1-bradykinin receptor antagonist[22,23] (BK-B1). This was accomplished in four synthetic steps starting from **1a** (instead of the 14 steps required in the original synthesis)[23] as shown in Scheme 5. In our first approach, aldehyde **3l** was treated with the lithium-enolate of ethyl acetate to furnish β-hydroxyester **7** in 79% yield. Oxidation of this compound to sulfone **8** was ineffective and the starting material was recovered unchanged after several days of treatment with *m*-CPBA. To circumvent this problem, we inversed the order of events: **3l** was oxidized efficiently to sulfone **9**, obtained in 94% as a white crystalline solid. Addition of the lithium-enolate of ethyl acetate to this compound furnished **8** in 82% yield. Finally, facile basic hydrolysis of the ester function gave the sulfone **10** in 88% yield, after crystallization from chloroform.

In summary, a new Brønsted acid-catalyzed C4–C3 ring contraction reaction has been established which allows access to arylthio- and arylselenyl-functionalized cyclopropyl carbaldehydes and ketones from 2-hydroxycyclobutanone derivatives. The transformation is achieved *via* a cascade, metal-free process under mild conditions in which electronic effects of the cyclobutanone species play a crucial role in the ring-contraction/ring opening process.[19–21]



Scheme 5 Formal synthesis of the anti-inflammatory BK-B1 receptor antagonist, **11**.

To the best of our knowledge, there is no literature precedent for this transformation; most known synthetic methods proceed *via* pre-formed arylthiocyclopropane intermediates.[11–13] The efficient access to compound **10**, the known precursor of a biologically active compound, suggests that this synthetic methodology may be of interest for the preparation of other multifunctional cyclopropane derivatives as building blocks in medicinal chemistry.

Conflicts of interest

There is no conflict of interest regarding this paper.

Notes and references

1 J. J. Bloomfield and J. M. Nelke, *Org. Synth.*, 1988, **6**, 167.
2 (*a*) J. C. Namsylo and D. E. Kaufmann, *Chem. Rev.*, 2003, **103**, 1485; (*b*) E. Lee-Ruff and G. Mladenova, *Chem. Rev.*, 2003, **103**, 1449; (*c*) E. Lee-Ruff, *The Chemistry of Cyclobutanes*, ed. Z. Rappoport and J. F. Liebman, Wiley, Chichester, 2005, p. 281; (*d*) J. Salaün, *Sci. Synth.*, 2004, **26**, 557; (*e*) F. Secci, A. Frongia and P. P. Piras, *Molecules*, 2013, **18**, 15541; (*f*) S. Chen, G. Shan, P. Nie and Y. Rao, *Asian J. Org. Chem.*, 2015, **4**, 16.
3 M. Ohno, L. Oguri and E. Shoji, *J. Org. Chem.*, 1992, **64**, 8995.
4 R. W. Saalfrank, W. Hafner, J. Markmann, A. Welch, K. Peters, G. Hans and Z. Naturforsch, *J. Chem. Sci.*, 1994, **49**, 389.
5 S. Danappe, A. Pal, C. Alexandre, A. M. Aubertin, N. Bourgougnon and F. Huet, *Tetrahedron*, 2005, **61**, 5782.
6 (*a*) N. Melis, F. Secci, T. Boddaert, D. J. Aitken and A. Frongia, *Chem. Commun.*, 2015, **51**, 15272; (*b*) A. Martis, A. Luridiana, A. Frongia, M. Arca, G. Sarais, D. J. Aitken, R. Guillot and F. Secci, *Org. Biomol. Chem.*, 2017, **15**, 10053.
7 (*a*) D. J. Aitken, F. Capitta, A. Frongia, J. Ollivier, P. P. Piras and F. Secci, *Synlett*, 2011, 712; (*b*) D. J. Aitken, F. Capitta, A. Frongia, J. Ollivier, P. P. Piras and F. Secci, *Synlett*, 2012, 727.
8 (*a*) D. J. Aitken, P. Caboni, H. Eijsberg, A. Frongia, R. Guillot, J. Ollivier, P. P. Piras and F. Secci, *Adv. Synth. Catal.*, 2014, **356**, 941; (*b*) A. Frongia, N. Melis, I. Serra, F. Secci, P. P. Piras and P. Caboni, *Asian J. Org. Chem.*, 2014, **3**, 378; (*c*) N. Melis, L. Ghisu, R. Guillot, P. Caboni, F. Secci, D. J. Aitken and A. Frongia, *Eur. J. Org. Chem.*, 2015, 4358.
9 L. Ghisu, N. Melis, F. Secci, P. Caboni and A. Frongia, *Tetrahedron*, 2016, **72**, 8201.
10 (*a*) A. F. Vaquer, A. Frongia, F. Secci and E. Tuveri, *RSC Adv.*, 2015, **5**, 96695; (*b*) A. Luridiana, A. Frongia, D. J. Aitken, R. Guillot, G. Sarais and F. Secci, *Org. Biomol. Chem.*, 2016, **14**, 3394.
11 (*a*) H. Stadler, *Helv. Chim. Acta*, 2015, **98**, 1189; (*b*) B. B. Snider and M. Walner, *Tetrahedron*, 1989, **45**, 3171; (*c*) K. E. Harding, J. B. Strickland and J. Pommerville, *J. Org. Chem.*, 1988, **53**, 4877; (*d*) J. M. Conia and J. Salaun, *Acc. Chem. Res.*, 1972, **5**, 33.
12 (*a*) J. P. Barnier, J. M. Denis, J. Salaun and J. M. Conia, *Tetrahedron*, 1974, **30**, 1397; (*b*) V. Ghembus, L. Karmazin, S. Pira and D. Uguen, *Bull. Chem. Soc. Jpn.*, 2018, **91**, 319.
13 (*a*) B. M. Trost, W. C. Vladuchick and A. J. Bridges, *J. Am. Chem. Soc.*, 1980, **102**, 3548; (*b*) B. M. Trost and L. Jungheim, *J. Am. Chem. Soc.*, 1980, **102**, 7910.
14 (*a*) T. Cohen, W. M. Daniewski and R. B. Weisenfeld, *Tetrahedron Lett.*, 1978, **47**, 4665; (*b*) A. M. Bernard, A. Frongia, P. P. Piras, F. Secci and M. Spiga, *Org. Lett.*, 2005, **7**, 4565.
15 (*a*) K. Tanaka, H. Uneme, S. Matsui, R. Tanikaga and A. Kaji, *Chem. Lett.*, 1980, 287; (*b*) A. M. Bernard, E. Cadoni, A. Frongia, P. P. Piras and F. Secci, *Org. Lett.*, 2002, **4**, 2565; (*c*) A. M. Bernard, A. Frongia, R. Guillot, P. P. Piras, F. Secci and M. Spiga, *Org. Lett.*, 2007, **9**, 541.
16 Regarding the tendency of alkylthiols to produce of 2-sulfanylcyclobutanones **5** (Scheme 2), we suppose that kinetic effects and differences in the ability of alkyl and aryl sulfur derivatives to stabilize a positive charge in cyclobutylthionium ions are consequential in this transformation.
17 W. H. Urry and D. J. Trecker, *J. Am. Chem. Soc.*, 1961, **84**, 118.
18 ^{18}O-**1a** was prepared as described in the ESI.† Reaction of this compound with thiophenol **2a** (1.0 equiv.) in the presence of PTSA (20 mol%) afforded the corresponding carbaldehyde ^{18}O-**3a** in 92% yield (^{18}O incorporation 78%). See ESI† for details.
19 L. A. Paquette and J. E. Hofferberth, *The α-Hydroxy Ketone (α Ketol) and Related Rearrangements*, 2003, pp. 477–567.
20 (*a*) H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151; (*b*) J.-I. Matsuo, *Tetrahedron Lett.*, 2014, **55**, 2589; (*c*) Y. A. Volkova, E. M. Budynina, A. E. Kaplun, O. A. Ivanova, A. O. Chagarovskiy, D. A. Skvortsov, V. B. Rybakov, I. V. Trushkov and M. Y. Melni-kov, *Chem. – Eur. J.*, 2013, **19**, 6586; (*d*) O. A. Ivanova, E. M. Budynina, A. O. Chagarovskiy, I. V. Trushkov and Y. Melnikov, *J. Org. Chem.*, 2011, **76**, 8852; (*e*) J.-I. Matsuo, S. Sasaki, T. Hoshikawa and H. Ishibashi, *Org. Lett.*, 2009, **17**, 3822; (*f*) J.-I. Matsuo, R. Okado and H. Ishibashi, *Org. Lett.*, 2010, **12**, 3266; (*g*) A. M. Bernard, A. Frongia, P. P. Piras, F. Secci and M. Spiga, *Org. Lett.*, 2005, **7**, 4565; (*h*) G. Alberti, A. M. Bernard, C. Floris, A. Frongia, P. P. Piras, F. Secci and M. Spiga, *Org. Biomol. Chem.*, 2009, **7**, 3512.
21 Ring contraction of cyclobutanone **1e** was carried out by using CSA (ee > 99%) as a catalyst, yielding the corresponding cyclopropyl-derivative *trans*-**6e** as a racemic mixture.
22 (*a*) For reviews on bradykinin receptors and therapeutic targets see: J. Howl and S. J. Payne, *Expert Opin. Ther. Targets*, 2003, **7**, 277; (*b*) D. Regoli and J. Barabé, *Pharmacol. Rev.*, 1980, **32**, 1.
23 B. C. Askew, T. Aya, K. Biswas, J. J. Chen, H. J. Brooks and Q. Wenyuan, *Substituted sulfones and methods of use*, WO 2006041888, 2006.

