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Carboxylate-stabilised sulfur ylides (thetin salts) in asymmetric epoxidation for the synthesis of glycidic acids. Mechanism and implications

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The reaction of carboxylate-stabilised sulfur ylides (thetin salts) with aldehydes and ketones has been investigated. Using both achiral and chiral sulfur ylides, good yields were obtained with dimsylsodium or LHMDS as bases in DMSO or THF–DMSO mixtures. However, the enantioselectivities observed with a camphor-based sulfide were only moderate (up to 67%). The reaction was studied mechanistically by independent generation of the betaine (*via* the hydroxyl sulfonium salt) in the presence of a more reactive aldehyde, which resulted in incorporation of the more reactive aldehyde and showed that betaine formation was reversible. Thus, the moderate enantiomeric excess observed is a consequence of the enantiodifferentiating step being the ring closure step rather than the betaine forming step. We had expected betaine formation might be non-reversible because a carboxylate-stabilised ylide has only slightly higher stability than a phenyl-stabilised ylide, which does largely react non-reversibly with aldehydes. Evidently, a carboxylate-stabilised ylide is significantly more stable than a phenyl-stabilised ylide and as such reacts reversibly with aldehydes.

Introduction

Glycidic acids, esters and amides are extremely useful synthetic intermediates since they can be opened by nucleophiles with complete stereo- and often excellent regio-control to give highly functionalised compounds.[1] The most direct route to such compounds is *via* a Darzens-type reaction. This reaction involves an initial aldol reaction and it is therefore not surprising that the widespread asymmetric developments in the aldol area have been extended to Darzens reactions. Indeed, high enantioselectivity has been achieved by employing either chiral auxiliaries,[2] chiral reagents[3] or chiral catalysts.[4] Invariably, these reactions involve two discrete steps: the aldol reaction, followed by ring closure. In contrast, sulfur ylides react directly with aldehydes to give epoxides[5] and, recently, high enantioselectivity (95%–>99% ee) has been achieved with tertiary amide-stabilised ylides leading to an enantioselective route to glycidic amides (Fig. 1).[6] However, tertiary amides are difficult to convert into other acid derivatives. As such, we have investigated alternative ylides and in this paper we describe our studies employing carboxylate-stabilised sulfur ylides.

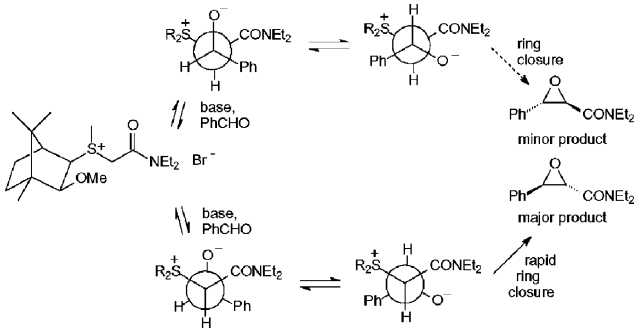
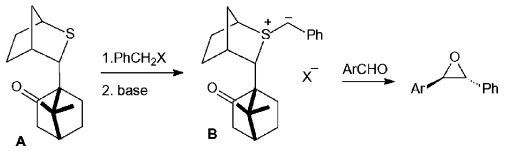


Fig. 1 Epoxidation by tertiary amide-stabilised ylides.

Our detailed mechanistic analysis of phenyl-stabilised ylides **B** has shown that partially reversible formation of the *syn*-betaine and non-reversible formation of the *anti*-betaine contributed to the excellent selectivities observed (up to >99% ee and 95% dr) (Scheme 1).[7]



Scheme 1 Epoxidation using optimised sulfide **A**.

In contrast, reversible formation of betaines derived from tertiary amide-stabilised ylides again gave excellent results (between 95%–>99% ee). Only the *trans*-diastereomer was formed when aromatic aldehydes were employed, but this turned out to be a special case. In this unique case, high enantioselectivity was the result of one diastereomer of the betaine undergoing ring closure more rapidly than the other (Fig. 1, lower pathway). In designing chiral sulfides for asymmetric epoxidation reactions it is very difficult to engineer features that affect the rates of ring closure of diastereomeric betaines. It is much easier to incorporate features that control which betaine diastereomer is formed, as demonstrated in the case with phenyl-stabilised ylides. Thus, if betaine formation could be made non- or partially reversible, our current optimum sulfide **A** should deliver high enantioselectivity. The degree of reversibility of betaine formation relates to ylide stability, a measure of which can be obtained from pK_a values of the corresponding sulfonium salts. We obviously needed a carbonyl group that stabilised the ylide to a similar extent as a phenyl group. We particularly considered a carboxylate group because such ylides had previously been employed in epoxidations with both aldehydes and ketones.[8] However, no pK_a values were available for this system and in fact very few pK_a's of sulfonium salts have been measured (Table 1).

In order to determine the relative stabilities of various ylides, we calculated the equilibrium between the trimethylsulfonium ylide and substituted sulfonium salts using the B3LYP 6-31G* base set with THF as solvent (Table 1). In descending the table betaine formation becomes more reversible, ylide stability increases and, ultimately, no reaction is observed (Table 1, entry 6, 7) as the ylide is too stable. This clearly showed the relationship between ylide stability and reversibility in betaine formation. It also showed that a sodium-carboxylate substituted ylide was the closest in stability to a phenyl substituted ylide. We therefore

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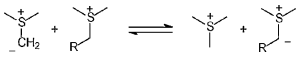
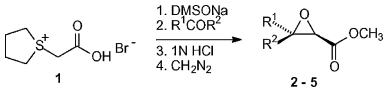
Table 1 Relative stability of ylides and their reactivity[a]



Entry	Substituent	pK_a	ΔE/kcal mol^{-1}	Reactivity/explanation [towards aldehydes]
1	H	—	0.00	Epoxide formation; betaine formation non-reversible
2	Ph	17.9[b9]	−9.90	Epoxide formation; betaine formation partially-reversible
3	CO_2Na	—	−11.85	Epoxide formation known
4	CO_2Li	—	−17.22	Epoxide formation known
5	$CON(CH_3)_2$	—	−21.74	Epoxide formation; betaine formation fully reversible
6	CO_2CH_3	—	−27.58	No reaction (ylide too stable)
7	C(O)Ph	8.45 [c10]	−30.07	No reaction (ylide too stable)

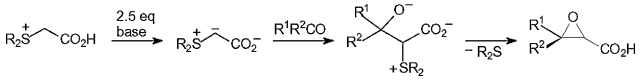
[a] Calculations carried out with a B3LYP 6-31G* base set. [b] In DMSO. [c] In 80% EtOH.

Table 2 Scope of electrophiles



Entry	Carbonyl compound	R^1	R^2	Yield (%)	Ester
1	Cyclohexyl-carboxaldehyde	Cy	H	98	**2**
2	Pentanal	$CH_3(CH_2)_3$	H	73	**3**
3	Trifluoromethyl-benzaldehyde	$pCF_3(Ph)$	H	75	**4**
4	Cyclohexanone	$(CH_2)_5$		68	**5**

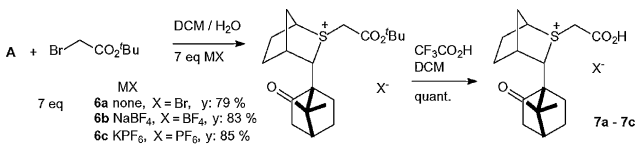
considered the use of carboxylate-stabilised ylides in order to broaden the scope of our asymmetric epoxidation process (Scheme 2).



Scheme 2 General reaction pathway for the formation of glycidic acids.

Results and discussion

In our initial studies we prepared tetrahydrothiophene thetin salts in order to optimise the reaction conditions and to establish the range of electrophiles suitable for this transformation (Table 2). Excellent yields of the *trans*-substituted glycidic esters could be obtained with a wide range of electrophiles, including α-branched aliphatic (Table 1, entry 1), unbranched aliphatic (Table 1, entry 2) and aromatic aldehydes (Table 1, entry 3), as well as ketones (Table 1, entry 4), using dimsylsodium as a base in DMSO at room temperature followed by esterification. This reaction was highly diastereoselective, furnishing the *trans*-epoxide only. Having established conditions and suitable substrates for the epoxidation we sought to render the reaction asymmetric and turned to our camphor-derived sulfide **A** (Scheme 3). The required sulfonium salts **7** bearing different counter ions were prepared as shown in Scheme 3.



Scheme 3 Synthesis of the sulfonium salt **7**.

Commercially available α-bromo-*tert*-butyl-acetate was reacted with sulfide **A** in a biphasic environment (with aqueous saturated salt solutions to achieve concomitant counter ion exchange) and the sulfonium salts **6** were obtained in high yields. Although the direct formation of the sulfonium salt with α-bromo-acetate had been previously reported,[11] the sulfides were always utilised in excess, even as the solvent, which was not appropriate in this case. In our synthesis of the sulfonium salts, the use of only one equivalent of the chiral sulfide **A** and an easy exchange of the counter ion (Br^- *versus* BF_4^- or PF_6^-) are particularly noteworthy. The hygroscopic thetin salts **7** are prone to decarboxylate.[12] In fact, Forbes *et al.* applied this thermally induced loss of carbon dioxide to generate methylsulfonium salts for base-free epoxidations.[13] We found it more convenient to store the stable, less hygroscopic esters **6** at room temperature and convert them into the thetin salts **7** when needed. Structure determination was substantiated by X-ray crystallography of **7b**†‡ (Fig. 2).

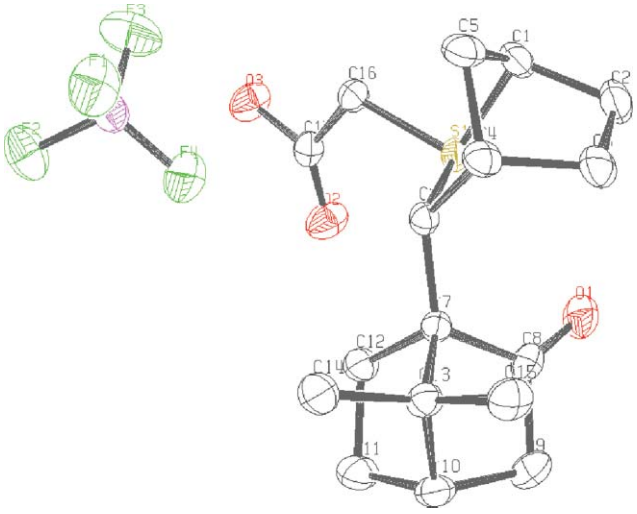
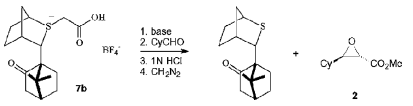


Fig. 2 X-ray structure of (+)-**7b** [ORTEP].

† CCDC reference number 258338. See http://www.rsc.org/suppdata/ob/b4/b418740g/ for crystallographic data in CIF or other electronic format.

‡ The salt for X-ray structure determination was obtained from the opposite enantiomer of **A**.

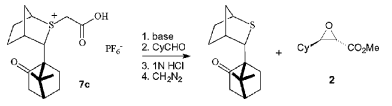
Table 3 Darzens-type reaction of **7b**



Entry	Base (2.5 eq.)	Solvent	Temp./°C	Yield (%)	dr	Enantiomeric excess (%)[a]
1	DMSONa	DMSO	20	80	>99 : 1	25
2	LHMDS in toluene	THF–DMSO	0	82	>99 : 1	33
3	LHMDS in toluene	THF	−40	8	>99 : 1	56
4	KHMDS in THF	THF–DMSO	−45	9	>99 : 1	58
5	KHMDS with 18-crown-6	THF	−45	10	>99 : 1	59

[a] Determined by chiral GC, absolute stereochemistry of major product is shown in Scheme 4.

Table 4 Darzens-type reaction of **7c**



Entry	Base (2.5 eq.)	Solvent[a]	Temp./°C	Yield (%)	dr	Enantiomeric excess (%)
1	P_2base	DCM	−80 to 0	9	>99 : 1	53
2	LHMDS	THF	−50	8	>99 : 1	67
3	LDA	THF	−75	9	>99 : 1	54
4	KHMDS[b]	toluene[c]–dioxane	15 °C then 0 °C	64	>99 : 1	35

[a] Concentration 0.04 (mol l^{-1}). [b] 2.5eq. 18-crown-6 was used as additive. [c] Concentration was 0.02 (mol l^{-1}).

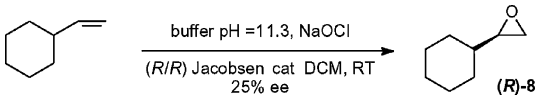
Asymmetric epoxidation process

Initial investigations were carried out with salt **7b** using cyclohexanecarboxaldehyde (CyCHO) as the electrophile with a variety of bases and solvents (Table 3). It was found that the highest yields were obtained in the dipolar aprotic solvent DMSO (Table 3, entry 1, 2), but enantiomeric excesses were low. By using a mixture of THF and DMSO (1 : 1) with a lithium base, we were able to conduct the reaction at lower temperatures which led to a small increase in enantiomeric excess (Table 3, entry 2). Further temperature reduction was possible using THF alone (Table 3, entry 3). Under these conditions, the ylide was not completely in solution and it proved difficult to obtain good yields. The expected increase in enantiomeric excess by employing potassium ylides was not realised (Table 3, entry 4, 5), as the potassium ylides were expected to react less reversibly because the potassium carboxylate is less anion stabilised than other metal carboxylates (see Table 1, entry 3, 4). Other variations in reaction parameters, including change of solvent, temperature and additives, did not lead to further improvements in yield or enantiomeric excess.§

As the BF_4 salt **7b** showed limited solubility, the PF_6 salt **7c** was also examined to see if yield or enantioselectivity could be improved by changing the counter ion. However, no significant improvements in either were observed (Table 4).

Without a strong chromophore in epoxide **2**, we had to resort to GC/MS and chiral GC analysis to determine enantioselectivity. The results from GC/MS indicated that decarboxylation had occurred during analysis (most probably in the injector port) as the molecular ion peak of the terminal epoxide **8** was observed (Scheme 4).

To verify this, (*R*)-**8** was synthesised by an independent route using the Jacobsen protocol and the retention times of (*R*)-**8** and **2** were compared.[14] These were identical, thus confirming our understanding of the processes occurring during analysis and establishing for the first time the absolute stereochemistry of the glycidic esters obtained. A detailed explanation of the origin of our enantioselectivity is given in Scheme 5 and is discussed later.



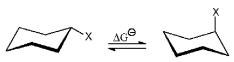
Scheme 4 Determination of absolute stereochemistry of **8**.

The lower than expected level of asymmetric induction observed in our epoxidations could result from either poor control in ylide conformation or reversibility in betaine formation (Scheme 5). We felt that ylide conformation would be well controlled because A-values¶ of a carboxylate and a phenyl group are comparable.[15] Since the conformation of the phenyl substituted ylide is well controlled,[7] we would therefore expect that the conformation of the carboxylate-stabilised ylide would be similarly well controlled. We therefore focussed on examining whether betaine formation was reversible or not.[16] This was achieved by independent preparation of the intermediate betaines and examining the stereospecificity of ring closure and carrying out cross-over experiments.[17]

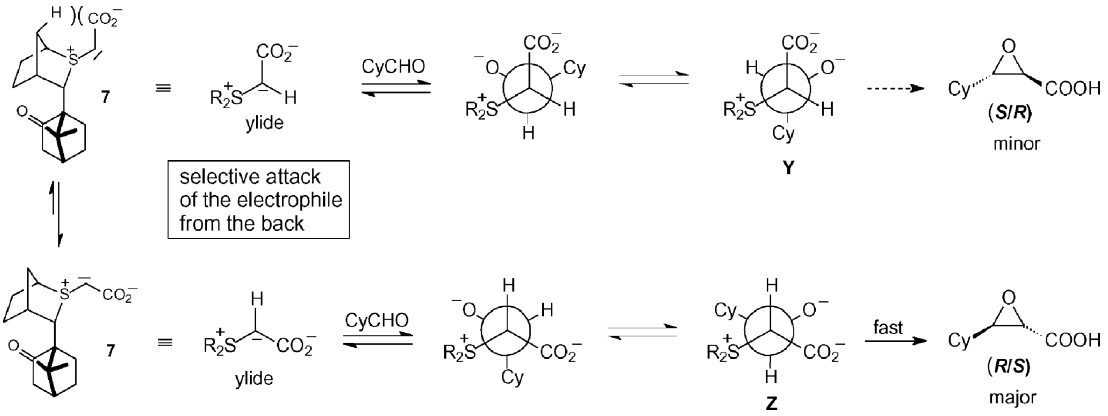
Synthesis of the betaines

The *syn*- and *anti*-sulfonium salts were synthesised as shown in Scheme 6. Substitution of the commercially available α-bromo-acetic-*tert*-butyl ester with sodium thiomethoxide gave α-thiomethoxy-acetic-*tert*-butylester (**9**) in 93% yield. An aldol reaction with cyclohexylcarboxaldehyde furnished a separable 2.4 : 1 mixture of diastereo isomers in favour of the *anti*-adduct **10**. The relative stereochemistry of the aldol adducts

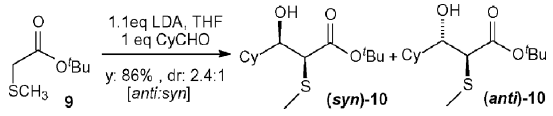
§ No product formation was observed in acetonitrile and dimethylformamide as solvent or when other bases, such as Grignard reagents, were employed. Chelating salts, such as $MgBr_2$ and $ZnCl_2$, did not lead to product formation either.

¶ 

Definition: A-value = $-\Delta G^{\ominus}$: A_{Ph} (−100 °C): 2.8 (kcal mol^{-1}); A_{COOH} (25 °C): 1.4 (kcal mol^{-1}); A_{COO^-} (25 °C): 2.0 (kcal mol^{-1}).



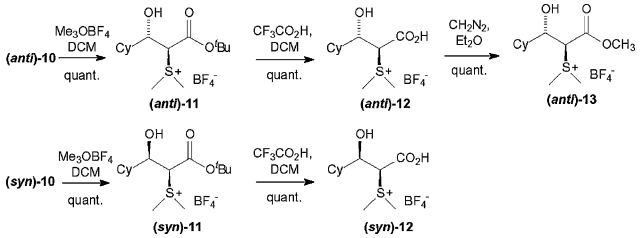
Scheme 5 Origin of enantioselectivity.



Scheme 6 Synthesis of hydroxyl dimethylsulfonium salts **10**.

were determined by comparison of the NMR *J*-values*[16] and diastereomeric ratios (*anti* : *syn*, 2 : 1)[17] by analogy to literature known compounds.

Alkylation of the sulfides (*syn*)-**10** and (*anti*)-**10** with Meerwein's reagent gave the sulfonium salts **11** (Scheme 7). It was critical to avoid traces of water, as the acid generated from its reaction with Meerwein's salt caused partial cleavage of the *tert*-butyl ester. An acid catalysed cleavage of the ester **11** yielded **12** quantitatively. As these salts were hygroscopic and difficult to analyse, small amounts of **12** were derivatised with diazomethane into the corresponding methyl esters **13** to prove their structure.

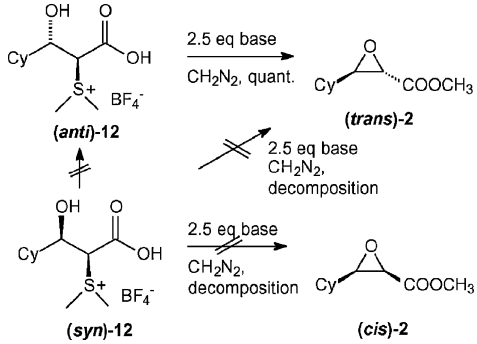


Scheme 7 Synthesis of hydroxy dimethylsulfonium salts **12**.

Mechanistic studies and results of the cross-over experiment

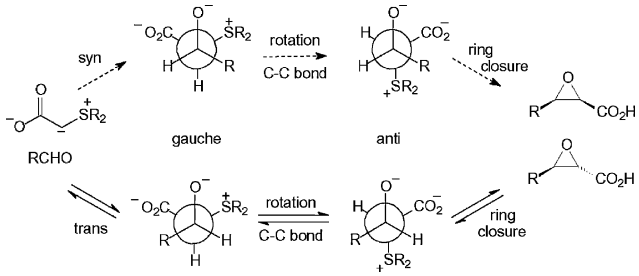
Before carrying out cross-over experiments, the *syn*- and *anti*-sulfonium salts **12** were treated with 2.5 eq. of base. If betaine formation was non-reversible, one would observe a stereospecific ring closure to give exclusively *cis*- and *trans*-epoxides, respectively.[17] In practice, the *anti*-betaine **12** gave (*trans*)-**2**, but treatment of the (*syn*)-**12** salt did not yield any of the expected *cis*-epoxide **2** (Scheme 8). The lack of formation of the *cis*-epoxide was frustrating but could be the result of decarboxylation of the epoxy-acid (a common side reaction), which is likely to be more facile for the *cis*-isomer. Indeed, only few examples of *cis*-epoxy acids are known in the literature, most of them derived from oxidation of the corresponding epoxy alcohol.[18]

To investigate the level of reversibility of the *trans*-betaine formation, a cross-over experiment was carried out using a more reactive aromatic trifluoromethyl benzaldehyde as the second competing electrophile. This experiment was designed to



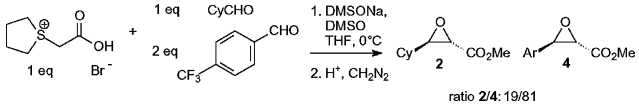
Scheme 8 Stereospecificity of ring closure.

investigate whether reversion to the starting materials (aldehyde and ylide) is faster than ring closure to the epoxide (Scheme 9).



Scheme 9 Origin of diastereoselectivity.

In a control experiment, the tetrahydrothiophene thetin sulfonium salt was treated with base and a mixture of two eq. of the more reactive aromatic aldehyde and one eq. of cyclohexanecarboxaldehyde (Scheme 10).



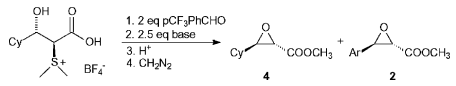
Scheme 10 Control experiment, maximal ratio of product.

A 19 : 81 ratio of the two epoxides (**2** : **4**) was obtained, incorporating the more reactive aromatic substituent preferentially. This result indicates that if the betaine formation is fully reversible, this is the maximum ratio one would expect in a cross-over experiment.

The cross-over experiments itself were conducted under the same reaction conditions as employed above to determine whether solvent polarity affected the outcome of the experiment. In DMSO a 20 : 80 ratio of epoxides (**2** : **4**) was obtained, showing that the reaction was fully reversible (Table 5, entry 1). Even using potassium salts in a mixture of less polar solvents (Table 5,

* *trans* Reported: 6.0 Hz, found 6.6 Hz; *cis* reported: 4.0 Hz, found 5.5 Hz.

Table 5 Cross-over experiment



Entry	Base (2.5 eq.)	Solvent	Temp./°C	Yield (%)	Ratio **2** : **4**
1	NaDMSO	DMSO	Rt	89	20 : 80
2	KHMDS[a]	THF–DMSO	0	63	33 : 77
3	KHMDS[a]	THF	−40	62	29 : 71

[a] In toluene using 2.5 eq. 18-crown-6 as additive.

entry 2) with crown ether to capture the potassium ion at reduced temperatures (Table 5, entry 3) still resulted in substantial reversibility and incorporation of the more reactive aldehyde. For obvious reasons, we did not carry out the cross-over experiments with the *syn*-betaine **12**, since no product formation was obtained even under the most suitable reaction conditions (dimsylsodium as base at rt) without any competing electrophile.

The reversibility in betaine formation implicates either bond rotation or the ring closure step as the enantiodifferentiating step. In related reactions involving amide-stabilised ylides, we have found that the ring closure step is most likely the rate determining step and so we assume that a similar scenario applies in this case. Thus, the overall mechanistic picture of the ylide reaction is best described by Scheme 5. A series of reversible steps leads to an equilibrium mixture of betaines **Y** and **Z** and the ratio of epoxides obtained depends on their relative concentration and rates of the ring closure (Curtin–Hammett).

Conclusions

Carboxylate-stabilised ylides react with aldehydes to give epoxides in good yields. The reaction can be rendered asymmetric using chiral sulfides, although enantioselectivities are relatively moderate. Detailed analysis of the reaction mechanism, primarily from generating the intermediate betaines in the presence of a more reactive aldehyde and observing cross-over products, has shown that betaine formation is fully reversible. This accounts for the low enantioselectivity observed. Thus, under our reaction conditions and irrespective of the counter ion employed, carboxylate-stabilised ylides should be regarded in the class of stabilised ylides rather than *semi*-stabilised ylides as the latter class react non- or partially reversibly with aldehydes whilst stabilised ylides react reversibly.

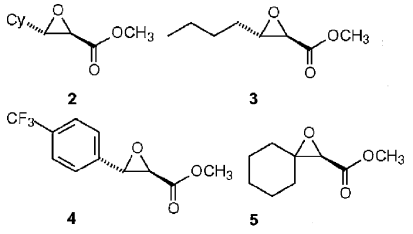
Experimental

General

Reactions requiring anhydrous conditions were performed in vacuum-dried glassware under an argon atmosphere using standard canula techniques. The solvents were purified after standard procedures. Liquid starting materials were distilled before use and solid compounds were used as supplied. P2-base (1-ethyl-2,2,4,4,4-pentakis(dimethylamino)-2l5,4l5-catenadi (phosphazene)) was supplied from Aldrich and used without purification. Chromatographic purification was achieved on silica gel (Merck, Kieselgel 60, 230–400 mesh) and the reactions were monitored by TLC on alumina backed silica plates ($60F_{254}$, 0.2 mm). Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. ^{1}H spectra were recorded at 400 MHz on a Jeol Eclipse 400 instrument. Chemical shifts (δ) are quoted in ppm and are referenced to TMS or, in the absence of the latter, to the solvent peak; J values are given in Hz. ^{13}C NMR spectra were recorded to 101 MHz on the same instrument and are referenced to the appropriate solvent peak. Elemental microanalyses were carried out using a Perkin Elmer 2400 CHN elemental analyser. HR-mass spectra were recorded using a Bruker Daltonics (Billerica, MA, USA) ApexIV 7Tesla FT-ICR-MS with Apollo Electrospray source. As a X-ray generator was used a standard water cooled W-filament source, which produces Mo K-alpha radiation and is typically used at 50 kV and 40 mA (2 kW power). The CCD (charge-coupled device) area detector has a two-dimensional array of photodiodes (1024 × 1024 elements) coupled by fibre-optics. The analytical data of literature known compounds were in good agreement with the data reported. Diastereomeric ratios were determined from the crude proton NMR spectra and enantiomeric excesses were determined by chiral GC (Supelco 120, gamma dex; 30 m × 0.25 mm × 0.25 μm). A gradient method was applied, 70 °C isotherm for 10 minutes and then heating with a rate of 1 °C per minute to 140 °C.

1-Carboxymethyl-tetrahydro-thiophenium bromide (1). Tetrahydrothiophene (19.4 ml, 220 mmol) and bromo-acetic acid (27.79 g, 200 mmol) were stirred in acetone (75 ml) under a nitrogen atmosphere for two days. The precipitate formed in acetone was collected by filtration, washed with cold diethyl ether (3 × 15 ml) and dried under a vacuum to give **1** as a white crystalline solid in 82% yield (37.21 g, 164.0 mmol). Mp 96–99 °C (decomp.); (found: M+, 147.0473. $C_6H_{11}O_2SBr$ 147.0479); (found C, 32.00; H, 5.04; S, 13.99%. $C_6H_{11}BrO_2S$ required C, 31.73; H, 4.80; S, 14.12%); ν_{max} (neat)/cm^{-1} 2805, 1714; δ_H (400 MHz, CD_3OD) 2.21–2.31 (4H, m, SCH_2CH_2), 3.48–3.57 (4H, m, SCH_2CH_2), 4.35 (2H, s, SCH_2CO_2). δ_C (101 MHz, CD_3OD) 28.2 (CH_2), 42.6 (CH_2), 50.0 (CH_2), 167.5 (C).

Method A. Standard epoxidation procedure with DMSONa as base: to a stirred solution of DMSONa (freshly prepared according to the literature procedure)[19] in 1 ml DMSO under nitrogen was added 113 mg carboxymethyl-tetrahydrothiophenium bromide over a period of five minutes. After stirring for 30 minutes the ylide was a pale solution and the electrophile (0.5 mmol) was added in one portion *via* a syringe. After 18 hours stirring at rt, the reaction mixture was diluted with diethyl ether and poured onto ice. After phase separation, the organic layer was washed once with ice cold saturated $NaHCO_3$ solution. The combined basic layers were acidified with ice cold 1 N HCl aq. to a pH of 2–3 and the product was re-extracted in the organic layer (three times) with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and exposed to an etherial solution of CH_2N_2 until no more nitrogen evolution was observed. The solvent was evaporated at a reduced pressure to yield aromatic-smelling oils. If purification was necessary, a Kugelrohr-distillation gave the final product.

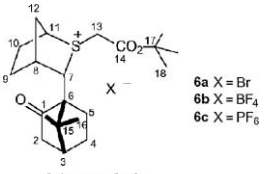


3-Cyclohexyl-oxirane-carboxylic-acid-methylester (2)[20]. This compound was prepared according to method **A** as colourless oil in 98% yield (83 mg, 0.49 mmol). ν_{max} (neat)/cm^{-1} 1746; δ_H (400 MHz, $CDCl_3$) 1.15–1.26 (5H, m, Cy), 1.69–1.77 (6H, m, Cy), 2.99 (1H, dd, $J = 6.4$ Hz, $J = 2.0$ Hz, C*H*Cy), 3.29 (1H, d, $J = 2.0$ Hz, C*H*CO), 3.79 (3H, s, CO_2CH_3). δ_C (101 MHz, $CDCl_3$) 25.4 (CH_2), 25.5 (CH_2), 26.1 (CH_2), 28.8 (CH_2), 29.3 (CH_2), 39.5 (CH), 51.9 (CH_3), 52.4 (CH), 62.6 (CH), 170.1 (CO). GC-analysis: t_R (*R*): 79.51; t_R (*S*): 79.98.

3-Butyl-oxirane-2-carboxylic-acid-methylester (3)[20]. This compound was prepared according to method **A** as colourless oil in 73% yield (58 mg, 0.37 mmol). ν_{max} (neat)/cm^{-1} 2975, 2929, 2862, 1758, 1742; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, $J = 7.3$ Hz, CH_3CH_2), 1.31–1.69 (6H, m, CH_2), 3.16 (1H, m, CH_2CHO), 3.23 (1H, d, $J = 1.9$ Hz, $CHOCO_2$), 3.79 (3H, s, CO_2CH_3). δ_C (101 MHz, $CDCl_3$) 13.9 (CH_3), 22.4 (CH_2), 27.8 (CH_2), 31.2 (CH_2), 52.4 (CH_3), 53.0 (CH), 58.6 (CH), 170.0 (CO).

3,4-(Trifluoromethyl-phenyl)-oxirane-2-carboxylic-acid-methylester (4)[21]. This compound was prepared according to method **A** as colourless oil in 75% yield (92 mg, 0.38 mmol). δ_H (400 MHz, $CDCl_3$) 3.49 (1H, d, $J = 1.7$ Hz, PhC*H*), 3.83 (3H, s, CO_2CH_3), 4.17 (1H, d, $J = 1.5$ Hz, C*H*), 7.42 (2H, d, $J = 8.3$ Hz, CF_3CCHCH), 7.63 (2H, d, $J = 8.3$ Hz, CF_3CCH). δ_C (101 MHz, $CDCl_3$) 52.7 (CH_3), 56.7 (CH), 57.1 (CH), 125.7 (C), 126.1 (2 × CH), 131.2 (CF_3, $J_{CF} = 33.1$ Hz), 138.9 (C), 168.1 (CO).

1-Oxa-spira[2,5]octane-2- carboxylic-acid-methylester (5)[8,22]. This compound was prepared according to method **A** as colourless oil [bp 138–142 °C; 20 mbar] in 68% yield (58 mg, 0.34 mmol). δ_H (400 MHz, $CDCl_3$) 1.38–1.78 (10H, m, Cy), 3.27 (1H, s, C*H*O), 3.71 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 24.8 (CH_2), 25.0 (CH_2), 25.3 (CH_2), 28.8 (CH_2), 34.9 (CH_2), 52.2 (CH_3), 59.4 (CH), 64.9 (C), 168.9 (CO)..

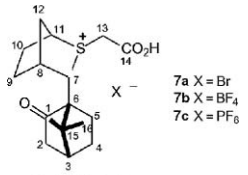


Salt esters 6a-6c

(1*S*,3*S*,4*R*)-2-*tert*-Butyloxymethyl-3-[(1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]-2-thioniabicyclo[2.2.1]heptane bromide (6a). To a stirred suspension of sulfide **A** (253 g, 1.00 mmol) in 1.4 ml of DCM and 2 ml of water was added α-bromo-*tert*-butyl-acetate (1.14 ml, 4.00 mmol) in one portion. The reaction mixture was stirred vigorously at rt and monitored by TLC for two days. After consumption of the sulfide, the reaction mixture was diluted with DCM and water (20 ml each). The resulting phases were separated, and the water layer was washed with DCM (3 × 10 ml). The combined organic washings were washed with brine (1 × 15 ml), dried over $MgSO_4$, filtered and the solvent was evaporated under a vacuum to yield 351 mg (0.79 mmol, 79% of the theory) of a white solid. $R_f = 0.11$ (75 : 25 petrol–EtOAc); mp 104–105 °C; $[\alpha]_D^{23} = -48.0$ ($c = 1.0$); (found: M+, 365.2148 $C_{21}H_{33}O_3S$ requires 365.2150); ν_{max} (neat)/cm^{-1} 3002, 2967, 1733, 1042; δ_H (401 MHz, $CDCl_3$) 1.12 (3H, s, $C^{16}H_3$), 1.23 (3H, s, $C^{16}H_3$), 1.39–1.53 (10H, m, C^5HH, $C^{18}H_3$), 1.55–1.78 (3H, m, C^5HH, C^9H_2), 1.98 (1H, d, $J = 18.6$ Hz, C^2HH), 2.09–2.38 (6H, m, C^3HH, C^4H_2, $C^{10}H_2$, $C^{12}HH$), 2.60 (1H, dd, $J = 18.6$ Hz, $J = 3.7$ Hz, C^2HH), 2.75 (1H, br. d, $J = 13.2$ Hz, $C^{12}HH$), 3.19 (1H, br. s, C^8H), 3.95 (1H, d, $J = 17.1$ Hz, $C^{13}HH$), 4.36 (1H, dd, $J = 17.1$ Hz, $C^{13}HH$), 4.42 (1H, br. s, C^7H), 4.46 (1H, d, $J = 5.4$ Hz, $C^{11}HH$). δ_C (125 MHz, CD_3OD) 19.2 (CH_3), 22.9 (CH_3), 24.3 (CH_2), 26.7 (CH_2), 26.8 (CH_2), 27.8 (3 × CH_3), 33.2 (CH_2), 40.8 (CH_2), 43.1 (CH), 44.0 (CH_2), 45.0 (CH), 45.6 (CH_2), 50.0 (C), 59.6 (C), 60.2 (CH), 67.4 (CH), 86.1 (C), 163.5 (CO), 215.7 (CO).

(1*S*,3*S*,4*R*)-2-*tert*-Butyloxymethyl-3-[(1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]-2-thioniabicyclo[2.2.1]heptane tetrafluoroborate (6b). To a stirred solution of the chiral sulfide **A** (1.02 g, 4.03 mmol) in 1.4 ml DCM was added α-bromo-*tert*-butyl-acetate (4.55 ml, 28.2 mmol) in one portion. 3.096 g (28.2 mmol) of $NaBF_4$ dissolved in 4 ml water (saturated solution) were added and the reaction mixture was stirred vigorously at rt and monitored by TLC for two days. After consumption of the sulfide, the reaction mixture was diluted with DCM and water. The resulting phases were separated and the water layer was washed with DCM (3 × 10 ml). The combined organic washings were washed with brine (1 × 15 ml), dried over $MgSO_4$, filtered and the solvent was evaporated under a vacuum to yield 1.50 g (3.35 mmol, 83% of the theory) of a white crystalline product. $R_f = 0.03$ (6 : 4 petrol–EtOAc); (found: M+, 365.2143 $C_{21}H_{33}O_3S$ requires 365.2145); mp 102–103 °C; mp 104–105 °C; $[\alpha]_D^{23} = -53.4$ ($c = 1.0$); (found C, 55.74; H, 7.33%; $C_{21}H_{33}BF_4O_3S$ requires C, 55.76; H, 7.33%); ν_{max} (neat)/cm^{-1} 2967, 1733, 1041; δ_H (500 MHz, CD_3OD, TOCSY, J_{res}.COSY) 1.02 (6H, s, $C^{16}H_3$), 1.39 (1H, m, C^5HH), 1.39 (9H, s, $C^{18}H_3$), 1.54–1.67 (2H, m, C^9H_2), 1.75 (1H, ddd, $J = 13.2$ Hz, $J = 8.9$ Hz, $J = 4.0$ Hz, C^5HH), 1.90 (1H, d, $J = 18.6$ Hz, C^2HH), 1.93 (1H, m, C^4HH), 2.00 (1H, m, C^4HH), 2.07 (1H, t, $J = 4.5$ Hz, C^3HH), 2.09–2.14 (2H, m, $C^{10}H_2$), 2.19 (1H, dt, $J = 12.6$ Hz, $J = 2.1$ Hz, $C^{12}HH$), 2.25 (1H, t, $J = 12.8$ Hz, $C^{12}HH$), 2.56 (1H, ddd, $J = 18.6$ Hz, $J = 4.9$ Hz, $J = 2.8$ Hz, C^2HH), 3.12 (1H, br. s, C^8H), 4.02 (1H, dd, $J = 3.4$ Hz, $J = 1.5$ Hz, C^7H), 4.33 (1H, br. s, $C^{11}H$). δ_C (125 MHz, CD_3OD) 19.8 (CH_3), 22.4 (CH_3), 25.6 (CH_2), 27.7 (CH_2), 27.9 (CH_2), 28.3 (3 × CH_3), 35.1 (CH_2), 42.1 (CH_2), 44.8 (CH), 45.0 (CH_2), 46.8 (CH), 49.8 (CH_2), 51.2 (C), 61.5 (C), 61.6 (CH), 70.8 (CH), 86.8 (C), 165.2 (CO), 217.2 (CO).

(1*S*,3*S*,4*R*)-2-*tert*-Butyloxymethyl-3-[(1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]-2-thioniabicyclo[2.2.1]heptane hexafluorophosphate (6c). To a stirred solution of the chiral sulfide **A** (507 g, 2.00 mmol) in 1.4 ml DCM was added α-bromo-*tert*-butyl-acetate (2.28 ml, 14.1 mmol) in one portion. An aqueous solution of KPF_6 (2.590 g, 14.1 mmol) in 4 ml water was added and the reaction mixture was stirred vigorously at rt and monitored by TLC for four days. After consumption of the sulfide, the reaction mixture was diluted with DCM and water. The resulting phases were separated and the water layer was washed with DCM (3 × 20 ml). The combined organic washings were washed with brine (1 × 15 ml), dried over $MgSO_4$, filtered and the solvent was evaporated under a vacuum to yield 772 mg (1.70 mmol, 85% of the theory) of an off-white solid. $R_f = 0.05$ (9 : 1 DCM–MeOH); $[\alpha]_D^{23} = -60.0$ ($c = 1.0$); (found: M+, 365.2148; $C_{21}H_{33}O_3S$ requires 365.2150); mp 101–102 °C; ν_{max} (neat)/cm^{-1} 3002, 2967, 1733, 1726, 1042; δ_H (400 MHz, CD_3OD) 1.12 (3H, s, $C^{16}H_3$), 1.22 (3H, s, $C^{16}H_3$), 1.40–1.54 (10H, m, 3 × $C^{18}H_3$, C^5HH), 1.64–1.73 (3H, m, C^5HH, C^9H_2), 2.00 (1H, d, $J = 18.8$ Hz, C^2HH), 2.11–2.27 (6H, m, C^4H_2, C^3H, $C^{10}H_2$, $C^{12}HH$), 2.34 (1H, m, $C^{12}HH$), 2.57–2.64 (1H, ddd, $J = 18.8$ Hz, $J = 4.6$ Hz, $J = 2.2$ Hz, C^2HH), 3.18 (1H, br. s, C^8H), 3.87 (1H, d, $J = 17.7$ Hz, $C^{13}HH$), 4.22 (1H, d, $J = 17.7$ Hz, $C^{13}HH$), 4.23 (1H, br. s, C^7H), 4.42 (1H, d, $J = 5.1$ Hz, $C^{11}H$). δ_C (101 MHz, $CDCl_3$) 19.1 (CH_3), 21.9 (CH_3), 24.3 (CH_2), 26.7 (CH_2), 26.8 (CH_2), 27.8 (3 × CH_3), 33.4 (CH_2), 40.8 (CH_2), 43.1 (CH), 44.0 (CH_2), 45.0 (CH), 45.7 (CH_2), 50.1 (C), 59.6 (C), 60.2 (CH), 68.2 (CH), 86.5 (C), 163.3 (CO), 215.6 (CO).



Salt acids 7a-7c

Standard procedure for ester cleavage

0.3 mmol of **6a** were dissolved in 0.15 ml of DCM under an argon atmosphere, before 0.10 ml of trifluoroacetic acid was added *via* a syringe in one portion. The reaction mixture was allowed to stir at rt for one hour. The crude mixture was diluted with diethyl ether until the product precipitated. After filtration of the ether under a protection atmosphere, the product was dried on a high vacuum pump, resulting in the desired products quantitatively as white, hygroscopic solids.

(1*S*,3*S*,4*R*)-2-Carboxymethyl-3-[(1*S*,4*R*)-7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl]-2-thioniabicyclo[2.2.1]heptane bromide (7a). According to the standard procedure, 116 mg (0.3 mmol) of **7a** were obtained of 134 mg (0.3 mmol) **6a** as a white solid; (found: M+, 309.1518; M + Na, 331.1340 $C_{17}H_{25}O_3S$ requires 309.1519, M + Na, 331.1338); mp 90–95 °C (decomp.); ν_{max} (neat)/cm^{-1} 3457, 2970, 1749; δ_H (400 MHz, CD_3OD) 1.08 (3H, s, $C^{16}H_3$), 1.09 (3H, s, $C^{16}H_3$), 1.47 (1H, m, C^5HH), 1.68–1.86 (3H, m, C^5HH, C^9H_2), 2.00–2.42 (8H, m, C^4H_2, C^2HH, C^3H, $C^{10}H_2$, $C^{12}H_2$), 2.65 (1H, ddd, J = 7.6 Hz, J = 2.0 Hz, J = 0.9 Hz, C^2HH), 3.23 (1H, br. s, C^8H), 4.24 (1H, dd, J = 3.3 Hz, J = 1.8 Hz, C^7H), 4.31 (1H, d, J = 16.6 Hz, $C^{13}HH$), 4.40 (1H, d, J = 16.6 Hz, $C^{13}HH$), 4.48 (1H, br. s, $C^{11}H$). δ_C (101 MHz, CD_3OD) 17.7 (CH_3), 20.2 (CH_3), 22.3 (CH_2), 23.4 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 32.8 (CH_2), 39.9 (CH_2), 42.6 (CH), 42.8 (CH_2), 44.6 (CH), 49.0 (C), 59.1 (C), 59.3 (C), 68.1 (CH), 165.2 (CO), 214.9 (CO).

(1*S*,3*S*,4*R*)-2-Carboxymethyl-3-[(1*S*,4*R*)-7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl]-2-thioniabicyclo[2.2.1]heptane tetrafluoroborate (7b). According to the standard procedure, 119 mg (0.3 mmol) **7b** were obtained from 136 mg (0.3 mmol) of **6b** as a white solid;† mp 91–95 °C (decomp.); ν_{max} (neat)/cm^{-1} 3224, 2980, 1736; (found: M+, 309.1522; M + Na, 331.1344 $C_{17}H_{25}O_3S$ requires 309.1519, M + Na, 331.1338); δ_H (400 MHz, CD_3OD) 1.16 (6H, s, $C^{16}H_3$), 1.47 (1H, m, C^5HH), 1.68–1.86 (2H, m, C^5HH, C^9HH), 1.84 (1H, td, J = 13.0 Hz, J = 3.9 Hz, C^9HH), 2.04 (1H, d, J = 18.8 Hz, C^2HH), 2.07–2.26 (6H, m, C^4H_2, C^3H, $C^{10}H_2$, $C^{12}HH$), 2.35 (1H, dt, J = 13.0 Hz, 1.0 Hz, $C^{12}HH$), 2.65 (1H, ddd, J = 18.8 Hz, J = 4.9 Hz, J = 2.2 Hz, C^2HH), 3.21 (1H, br. s, C^8H), 4.10 (1H, br. s, C^7H), 4.20 (1H, d, J = 16.9 Hz, $C^{13}HH$), 4.29 (1H, dd, J = 16.9 Hz, $C^{13}HH$), 4.45 (1H, br. s, $C^{11}H$). δ_C (101 MHz, CD_3OD) 19.8 (2 × CH_3), 22.4 (CH_2), 25.3 (CH_2), 27.8 (CH_2), 27.9 (CH_2), 35.0 (CH_2), 40.1 (CH_2), 41.9 (CH), 44.8 (CH_2), 45.0 (CH), 49.3 (C), 51.3 (C), 61.2 (C), 61.5 (CH), 165.8 (CO), 212.0 (CO).

(1*S*,3*S*,4*R*)-2-Carboxymethyl-3-[(1*S*,4*R*)-7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl]-2-thioniabicyclo[2.2.1]heptane hexafluorophosphate (7c). According to the standard procedure, 136 mg (0.3 mmol) of **7c** were obtained from 153 mg (0.3 mmol) of **6c** as a white solid; (found: M+, 309.1529; M + Na 331.1350; M + K 347.1091 $C_{17}H_{25}O_3S$ requires 309.1524); mp 89–94 °C (decomp.); ν_{max} (neat)/cm^{-1} 2975, 1736; δ_H (400 MHz, CD_3OD) 1.16 (3H, s, $C^{16}H_3$), 1.17 (3H, s, $C^{16}H_3$), 1.28 (2H, s, H_2O), 1.47 (1H, m, C^5HH), 1.65–1.87 (3H, m, C^5HH, C^9H_2), 2.01 (1H, d, J = 18.8 Hz, C^2HH), 2.07–2.23 (6H, m, C^4H_2, C^3H, $C^{10}H_2$, $C^{12}HH$), 2.27 (1H, dt, J = 12.7 Hz, J = 2.2 Hz, $C^{12}HH$), 2.39 (1H, br. d, J = 12.9 Hz, $C^{12}HH$), 2.65 (1H, ddd, J = 18.8 Hz, J = 4.6 Hz, J = 2.0 Hz, C^2HH), 3.21 (1H, br. s, C^8H), 4.16 (1H, dd, J = 3.2 Hz, 1.5 Hz, C^7H), 4.20 (less than 1H, br. s, $C^{13}HH$), 4.29 (less than 1H, br. s, $C^{13}HH$), 4.45 (1H, br. s, $C^{11}H$). δ_C (101 MHz, CD_3OD) 17.7 (CH_3), 20.2 (CH_3), 22.3 (CH_2), 23.4 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 32.8 (CH_2), 39.9 (CH_2), 42.6 (CH), 42.8 (CH_2), 44.5 (CH), 49.0 (C), 58.9 (C), 59.4 (C), 67.7 (CH), 168.9 (CO), 215.0 (CO).

Method B. Standard epoxidation procedure with LDA as base: to a solution of 131 µl of diisopropylamine (0.750 mmol) in 1.5 ml of THF at −78 °C was added dropwise 422 µl of a 1.6 molar solution of BuLi (0.675 mmol) in hexane. The freshly prepared LDA was allowed to stir for 15 minutes. In the meantime, 136 mg of **1** (0.33 mmol), which has been under a high vacuum for one hour prior to use, was suspended at rt in 5.5 ml dry THF in a 15 ml schlenk equipped with a magnetic stirrer bar. The schlenk was cooled down to −78 °C and the base was added dropwise over a period of ten minutes. After 12 minutes, 34 µl cyclohexyl-carboxaldehyde (0.33 mmol) were added in one portion and the reaction was stirred at −78 °C for six hours. The reaction mixture was diluted with diethyl ether, quenched with *ca.* 0.5 ml of methanol and 3 ml of water was added at 0 °C temperature. After phase separation, the organic layer was washed once with ice cold saturated $NaHCO_3$ solution. The combined basic layers were acidified with ice cold 1 N HCl aq. to pH = 2–3 and the product was re-extracted in the organic layer (three times) with diethyl ether and the combined organic layers were dried over $MgSO_4$, filtered and exposed to an etherial solution of CH_2N_2, until no more nitrogen evolution was observed. The solvent was evaporated at a reduced pressure to yield 5 mg (0.027 mmol, 9%) of an aromatic-smelling, colourless oil.

(*R*/*S*)-Cyclohexyloxirane (8)[23]. According to the literature, a solution of 0.05 M Na_2HPO_4 (5 ml) was added to a 12.5 ml solution of undiluted bleach. The pH was 12.0. This solution was cooled down to 0 °C and was added in one portion to an ice cold suspension of 127 mg of (*R*/*R*) Jacobsen catalyst and 684 µl (5 mmol) of vinylcyclohexene in 5 ml of DCM. The two-phase mixture was stirred vigorously and the ice bath was removed after 20 minutes. After 12 hours the reaction was quenched with 50 ml of water and 50 ml of hexane. After phase separation, the organic layer was washed with water (two times), brine (two times), dried over $MgSO_4$ and the solvent was removed under a vacuum. The NMR spectra were in agreement with the literature. The product was analysed *via* GC after filtration. γ-column t_R (*R*): 79.53; t_R (*S*): 79.98. δ_H (400 MHz, $CDCl_3$): 1.01–1.32 (6H, m, CH_2), 1.61–1.80 (4H, m, CH_2), 1.90 (1H, m, $C^{para}H$), 2.51 (1H, m, COH), 2.70 (2H, m, COH_2). δ_C (101 MHz, $CDCl_3$) 25.4 (CH_2), 25.5 (CH_2), 26.1 (CH_2), 28.2 (CH_2), 29.5 (CH_2), 40.2 (CH), 45.7 (CH_2), 56.4 (CH).

α-Thiomethoxy-acetic-*tert*-butylester (9)[24]. To a stirred suspension of 4.205 g of sodium thiomethoxide (60 mmol) in 80 ml of acetone was added *via* a dropping funnel 8.08 ml of α-bromoacetic-*tert*-butylester, diluted with 20 ml of acetone. The temperature rose during the addition to 40 °C. One cone end of a spatula with ammoniumtetramethyl iodide was added as a catalyst. The reaction was allowed to stir at 55 °C (oil bath) for 200 minutes. After cooling to rt, 100 ml of diethylester and 50 ml of water were added and the water layer was extracted three times with diethyl ether (25 ml each). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under a vacuum. Distillation of the crude residue at 54–55 °C/20 mbar afforded traces of the starting material and 5.880 g (93%, 46.6 mmol) of the product distilled over at 57–60 °C/20 mbar as a colourless, smelly liquid. ν_{max} (neat)/cm^{-1} 1722, 905; R_f = 0.29 (petrol–EtOAc 7 : 3); δ_H (400 MHz, $CDCl_3$) 1.48 (s, 9H, $C(CH_3)_3$), 2.21 (s, 3H, SCH_3), 3.10 (s, 2H, CH_2). δ_C (101 MHz, $CDCl_3$) 24.4 (CH_3), 26.6 (CH_3), 26.7 (CH_3), 30.1 (CH_3), 56.7 (C), 195.0 (CO), 207.0 (CO).

***syn–anti*-3-Cyclohexyl-3-hydroxy-2-methylsulfanyl-propionic-acid-*tert*-butylester (10).** To a stirred solution of diisopropylamine (1.18 ml, 8.43 mmol) in 14 ml of THF (abs.) was added at −35 °C 4.83 ml of *n*-BuLi (1.6 molar solution in hexane). The fresh prepared pale yellow LDA was allowed to stir for five minutes, before the cool bath was cooled down to −78 °C. 1.09 g (7.03 mmol) of α-thiomethoxyacetic-*tert*-butylester was dissolved in 20 ml THF in a second schlenk at a low temperature. The base was added dropwise over a period of ten minutes *via* a canula. The colour changed after addition of 1 eq. to orange. After addition of 935 µl (7.73 mmol) cyclohexylcarboxaldehyde, the colour of the mixture brightened

up to result in a yellow solution. The reaction was stirred at −78 °C for 1.45 hours and quenched with 3.85 ml of a 2 molar HCl solution in diethyl ether. The reaction was diluted with diethyl ether before removal of the ice bath. After addition of water, the phases were separated (aq. layer pH = 10) and the organic layer was washed with 0.1 molar aq. solution of $KHSO_4$ (two times), brine (once) and dried over $MgSO_4$. After filtration of the inorganic salts and evaporation of the solvent under a vacuum, the crude product was purified by column chromatography to result in 1.68 g of colourless oil. The dr (31.5 : 68.5) was determined by NMR proton spectrum of the crude product.

*(*syn*)-**10***. $R_f = 0.25$ (petrol–EtOAc 9 : 1); ν_{max} (neat)/cm^{-1} 3507, 2977, 2924, 2852, 1718; (found C, 61.55; H, 9.52; S, 11.79%. $C_{14}H_{26}O_3S$ required C, 61.28; H, 9.55; S, 11.68%); δ_H: (400 MHz, $CDCl_3$) 1.06–1.90 (20H, m, Cy, $C(CH_3)_3$), 2.19 (3H, s, SCH_3), 3.04 (1H, d, $J = 2.0$ Hz, O*H*), 3.18 (1H, d, $J = 5.8$ Hz, CHC*H*OH), 3.64 (1H, ddd, $J = J = 5.5$ Hz, $J = 1.5$ Hz C*H*CHOH). δ_C: (101 MHz, $CDCl_3$) 13.9 (CH_3), 26.0 (CH_2), 26.3 (CH_2), 27.1 (CH_2), 27.7 (CH_2), 27.9 (3 × CH_3), 29.8 (CH_2), 40.4 (CH), 52.1 (CH), 73.2 (CH), 81.9 (C), 171.1 (CO).

*(*anti*)-**10***. $R_f = 0.16$ (petrol–EtOAc 9 : 1); ν_{max} (neat)/cm^{-1} 3508, 2977, 2853, 2924, 1714; (Found C, 61.60; H, 9.57; S, 11.41%. $C_{14}H_{26}O_3S$ required C, 61.28; H, 9.55; S, 11.68%. δ_H (400 MHz, $CDCl_3$) 1.10–1.80 (20H, m, Cy, $C(CH_3)_3$), 2.18 (3H, s, SCH_3), 2.68 (1H, d, $J = 7.6$ Hz, O*H*), 3.25 (1H, br. d, $J = 6.6$ Hz, CHC*H*OH), 3.62 (1H, dd, $J = 12.5$ Hz, $J = 6.6$ Hz C*H*CHOH). δ_C (101 MHz, $CDCl_3$) 14.6 (CH_3), 25.9 (CH_2), 26.3 (CH_2), 26.3 (CH_2), 27.1 (CH_2), 30.0 (CH_2), 28.1 (3 × CH_3), 40.9 (CH), 50.8 (CH), 75.9 (CH), 80.2 (C), 171.6 (CO).

***anti-tert*-Butoxycarbonyl-2-cyclohexyl-2-hydroxy-ethyl)-dimethylsulfonium tetrafluoroborate (*anti*)-(11).** Under argon, 74 mg of trimethyloxonium-tetrafluoroborate were weighed out in a glove box in a schlenk and were suspended in 2.5 ml dry DCM. In a second oven dried flask was dissolved 124 mg of *syn*-3-cyclohexyl-3-hydroxy-2-methylsulfanyl-propionicacid-*tert*-butylester (0.5 mmol) in 3 ml of dry DCM under an argon atmosphere. The reaction was stirred overnight at rt. The resultant solution was frozen with liquid nitrogen and the solvent was removed under a high vacuum, to yield quantitatively an air sensitive white powder. The ester was over 95% pure and therefore was used in the next step without further purification and full characterisation. δ_H (400 MHz, CD_3OD) 0.89–2.24 (20H, m, Cy, $C(CH_3)_3$), 2.97 (3H, s, SCH_3), 3.00 (3H, s, SCH_3), 3.78 (1H, dd, $J = 9.0$ Hz, $J = 2.5$ Hz, C*H*S), 4.68 (1H, d, $J = 2.7$ Hz, C*H*OH).

***syn-tert*-Butoxycarbonyl-2-cyclohexyl-2-hydroxy-ethyl)-dimethylsulfonium tetrafluoroborate (*syn*)-(11).** Under argon, 74 mg of trimethyloxonium-tetrafluoroborate were weighed out in a glove box in a schlenk and were suspended in 2.5 ml of dry DCM. In a second oven dried flask was dissolved 124 mg of *syn*-3-cyclohexyl-3-hydroxy-2-methylsulfanyl-propionicacid-*tert*-butylester (0.5 mmol) in 3 ml of dry DCM under argon atmosphere. The reaction was stirred overnight at rt. The resultant solution was frozen with liquid nitrogen and the solvent was removed under a high vacuum, to yield quantitatively an air sensitive white powder. The ester was over 95% pure and therefore was used in the next step without further purification and full characterisation. δ_H (400 MHz, CD_3OD) 0.75–2.12 (20H, m, Cy, $C(CH_3)_3$), 2.91 (3H, s, SCH_3), 2.93 (3H, s, SCH_3), 3.92 (1H, dd, $J = 7.8$ Hz, $J = 5.1$ Hz, C*H*OH), 4.68 (1H, d, $J = 7.6$ Hz, C*H*S).

***anti*-Carboxy-2-cyclohexyl-2-hydroxy-ethyl)-dimethylsulfonium tetrafluoroborate (*anti*)-(12).** In an oven dried flask was dissolved 548 mg of *anti*-3-Cyclohexyl-3-hydroxy-2-methylsulfanyl-propionicacid-*tert*-butylester (2.21 mmol) in 3 ml of dry DCM. A solution of trimethyloxonium-tetrafluoroborate was added in one portion and the reaction was stirred overnight at rt. The resultant solution was frozen with liquid nitrogen and the solvent was removed under a high vacuum, to yield quantitatively an air sensitive white powder. ν_{max} (CD_3OD)/cm^{-1} 3558, 3022, 2931, 2859, 1702; δ_H (400 MHz, CD_3OD) 0.90–1.38 (5H, m, Cy), 1.67–1.91 (5H, m, Cy), 2.12 (1H, br. s, CyC*H*CHOH), 2.97 (3H, s, SCH_3), 3.01 (3H, s, SCH_3), 3.77 (1H, $J = 8.8$ Hz, $J = 2.9$ Hz, C*H*OH), 4.70 (1H, d, $J = 2.5$ Hz, C*H*S$(CH_3)_2$). δ_C (101 MHz, $CDCl_3$) 23.4 (CH_2), 25.1 (CH_2), 26.7 (2 × CH_3), 27.1 (CH_2), 29.9 (CH_2), 30.5 (CH_2), 42.6 (CH), 65.0 (CH), 74.1 (CH), 167.3 (CO).

***syn*-Carboxy-2-cyclohexyl-2-hydroxy-ethyl)-dimethylsulfonium tetrafluoroborate (*anti*)-(12).** As described above, the title compound was obtained quantitatively without further purification (NMR pure). ν_{max} (CD_3OD)/cm^{-1} 3339, 2469, 2243, 2216, 2070, 972; (found: M+, 233.1206; $C_{11}H_{21}O_3S$ requires 233.1206); δ_H (400 MHz, CD_3OD) 0.75–1.85 (11H, m, Cy), 2.91 (3H, s, SCH_3), 2.93 (3H, s, SCH_3), 3.92 (1H, d, $J = 7.8$ Hz, $J = 5.1$ Hz, C*H*OH), 4.48 (1H, d, $J = 7.6$ Hz, C*H*S$(CH_3)_2$). δ_C (101 MHz, $CDCl_3$) 22.5 (CH_2), 24.6 (CH_2), 25.9 (CH_2), 26.2 (CH_3), 26.3 (CH_3), 26.7 (CH_2), 29.5 (CH_2), 42.6 (CH), 60.6 (CH), 73.7 (CH), 166.7 (CO).

***anti*-Methoxycarbonyl-2-cyclohexyl-2-hydroxy-ethyl)-dimethylsulfonium tetrafluoroborate (*anti*)-(13).** The solvent of the NMR sample (*anti*)-**12**was removed under a high vacuum, the salt dissolved in few drops of acetic acid ethyl ester and acetone (1 : 1 mixture) and a freshly prepared etherical solution of CH_2N_2 was added until the yellow colour of the CH_2N_2 remained. The solution was stirred for 15 minutes and the solvent was removed under a high vacuum at rt; (found: M+, 247.1367 $C_{12}H_{23}O_3S$ requires 247.1368); ν_{max} (neat)/cm^{-1} 3463, 3017, 2970, 2857, 1741; δ_H (400 MHz, CD_3OD) 0.98–1.37 (5H, m, Cy), 1.68–1.89 (5H, m, Cy), 2.07 (1H, br. s., CyC*H*CHOH), 2.99 (3H, s, SCH_3), 3.02 (3H, s, SCH_3), 3.79 (1H, dd, $J = 9.3$ Hz, $J = 2.9$ Hz, C*H*OH), 3.91 (3H, s, $COOCH_3$), 4.76 (1H, d, $J = 2.9$ Hz, C*H*S$(CH_3)_2$). δ_C (101 MHz, $CDCl_3$) 22.7 (CH_2), 24.4 (CH_2), 26.1, (CH_3), 26.5 (2 × CH_3), 29.4 (CH_2), 29.9 (CH_2), 42.0 (CH), 64.4 (CH), 73.4 (CH_3), 73.5 (CH), 166.9 (CO).

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