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Bioinspired, Base- and Metal-Free, Mild Decarboxylative Aldol Activation of Malonic Acid Half Thioesters Under Phase-Transfer Reaction Conditions

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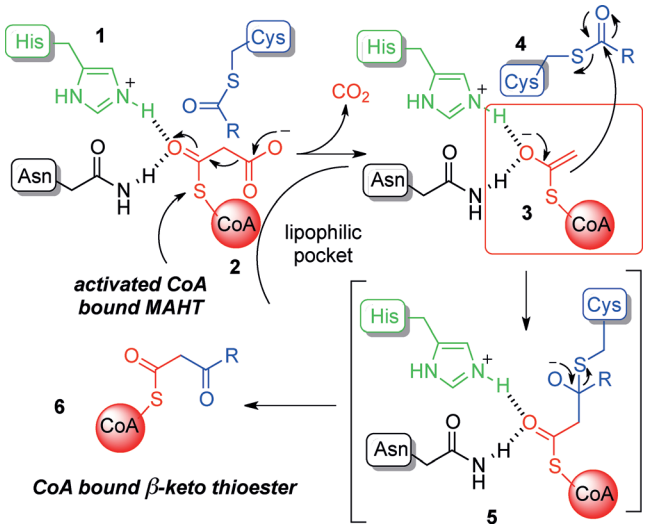
Abstract: Utilizing 'off the shelf' commercially available, cheap, small synthetic molecules that mimic the efficient mediation of important bioreactions utilized by Nature is not only highly sought after but also currently highly topical. This paper details our preliminary efforts at developing a unique *base- and metal-free* phase-transfer-mediated malonic acid thioester (MAHT) 'activation protocol' that efficiently generates (±)-β-thioesters. Our bioinspired aldol process is exceptionally mild, conducted under near neutral pH reaction conditions, does not require an inert, oxygen-free atmosphere or anhydrous reaction conditions and is highly atom-economic. Exemplifying the utility of our protocol, the synthesis of an array of structurally and functionally diverse (±)-β-hydroxy thioesters equipped with highly prized functionality, i.e., chlorine, bromine, fluorine, nitrile and nitro groups, is reported, as is the diastereoselective potential of this important reaction.

Keywords: aldol reaction; base-free conditions; decarboxylation; metal-free conditions; phase-transfer process

Introduction

Nature employs mild, ambient temperature, aqueous reaction conditions, polyketide synthase (PKS) and acetyl-CoA derived malonic acid half thioesters (MAHTs, see **2**, Scheme 1) as valuable building blocks for C–C bond formation. It is important to note that Nature's use of MAHTs in C–C bond formation proceeds *via* a 'non-metal, non-base' MAHT hydrogen bond-mediated 'activation' process. By way of an example employing aqueous conditions, the *Streptomyces* bacterium uses PKSs to generate structurally diverse and important bioactive metabolites such as rifamycin (antibiotic)[1] callystatin A (anticancer),[2] psymberin (anticancer),[3] pridamicin (antifungal)[4] and 6-deoxyerythrolide B (antiviral).[5] With the need for sustainable syntheses of entities such as these in mind, a significant motivating force for modern synthetic chemistry is the development of novel, environmentally green, laboratory-based C–C bond forming reactions that are also amenable to aqueous conditions and, importantly, proceed *via* 'non-metal, non-base' MAHT activation.[6]

In this paper we report, for the first time, an extremely mild 'non-metal, non-base' MAHT activation protocol that, similar to PKS,[7] proceeds in the presence of water and generates new C–C bonds *via* an essentially neutral decarboxylative aldol reaction. Not only is our phase-transfer-mediated MAHT activation unique, it is also amenable to a wide variety of structurally and functionally diverse aldehydes, employs cheap 'off the shelf' readily available, commercial quaternary ammonium salts and generates CO_2 as the only by-product. This, in conjunction with our recent-



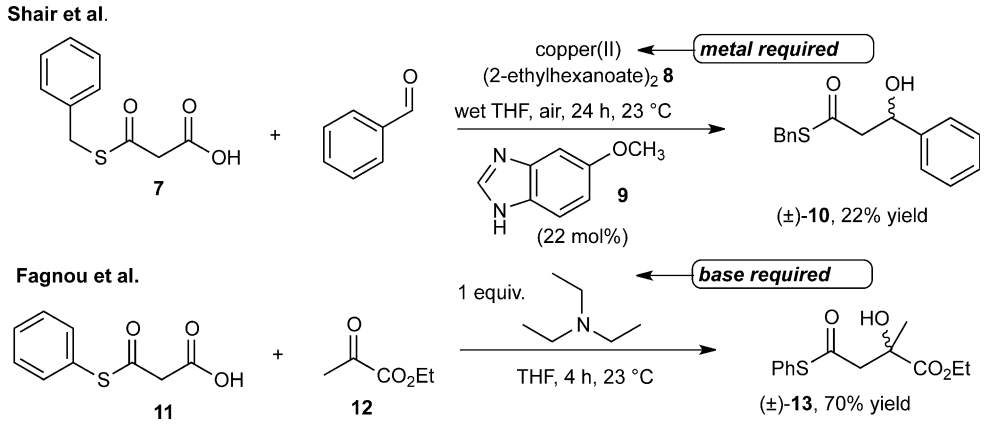
Scheme 1. Biosynthetic acetyl-CoA-derived MAHT 'activation', thioenolate formation and finally aldol condensation forming acetyl-CoA-bound β-keto thioester **6**.

ly reported two-step, solvent-free, multigram synthesis[8] of MAHTs, confers significant environmental benefits to our protocol over conventional base- or metal-mediated aldol reactions employing MAHTs.

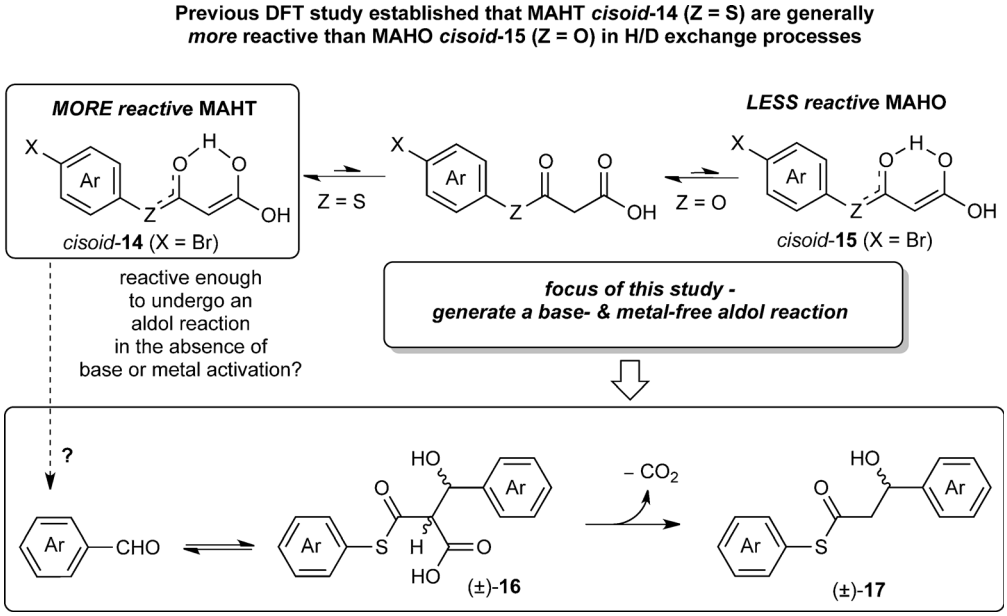
As noted, Nature generates a wealth of biologically active and diverse secondary metabolites *via* PKS biosynthesis.[9] Focusing in on their mode of action, PKSs are metal-free enzymes that contain an important triad of α-amino acids at their 'active site', i.e., His, Cys and Asp. Critical to the biosynthetic sequence of events is the requirement for both the Asp-derived $CONH_2$ group and the protonated histidine **1** to hydrogen-bond and 'activate' the carbonyl group of the β-thioester within the acetyl-CoA-derived MAHT anion (Scheme 1). When 'activated', **2** releases CO_2 generating within a lipophilic 'pocket' a thioenolate similar to **3**, this subsequently reacts with an adjacent cysteine-bound thioester **4** generating a tetrahedral species **5** which 'collapses' forming an acetyl-CoA bound β-keto thioester **6**.[10]

Over the last decade numerous groups have exploited the chemistry of 'activated' MAHTs in cutting edge transition metal[11] or base-mediated[12] aldol reactions. Thus Shair et al. described an elegant *metal*-mediated aldol reaction that afforded (±)-β-hydroxy thioesters from a selection of non-activated, activated, aliphatic or aromatic aldehydes and their reaction with copper(II) (2-ethylhexanoate) **8**, 5-methoxybenzimidazole **9** and 3-benzylthio-3-oxopropanoic acid **7**.[11d] By way of example, non-activated benzaldehyde afforded *S*-benzyl (±)-3-hydroxy-3-phenylpropanethiolate **10** in a 22% yield (Scheme 2). Similarly elegant work reported by Fagnou et al. involved the *base*-mediated activation of MAHT **11** and its aldol reaction with the electron-poor ketone in ethyl pyruvate **12**. Thus, incorporating[12f] one equivalent of triethylamine, 3-thiophenyl-3-oxopropanoic acid (**11**) and **12**, the initially formed addition adduct (not shown) subsequently underwent decarboxylation affording (±)-**13** in a 70% yield.

During our recent studies on developing efficient routes to MAHTs and MAHOs we identified *significant* reaction rate *enhancements* for hydrogen/deuterium (H/D) exchanges within certain *aryl* thioester MAHTs. A considerably smaller effect was observed for aryl ester-derived MAHOs. By way of example, MAHT **14** (X = Br) underwent an H/D exchange with a *k* of 208 whilst its chalcogen analogue MAHO **15** (X = Br) had a *k* of only 31.[8] With a view to establishing the origins of this significant rate difference (for the seemingly trivial S to O exchange) a 'benchmark' DFT study concluded that the rate enhancement associated with the MAHTs was associated with *increased* delocalization of the sulfur lone-pair into the adjacent carbonyl group affording greater levels of the *more* reactive enol-forms, i.e., *cisoid* **14** (Scheme 3) and the corresponding *transoid* form (not shown). In contrast, within MAHOs the analogous



Scheme 2. Metal- and base-activated MAHT incorporating aldol reactions generating (±)-**10** and (±)-**13**, respectively.

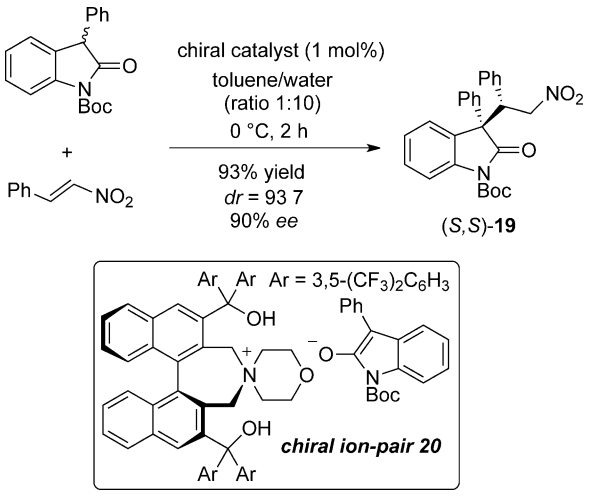


Scheme 3. A 'benchmarked' DFT study confirmed the enhanced reactivity of aryl-substituted MAHTs. i.e., *cisoid*-**14** in H/D exchange. This study proposes to exploit the *enhanced* reactivity of MAHT's developing a base- and metal-free aldol reaction affording entities based on (±)-**17**

oxygen atom was not so effective at donating its lone pairs, consequently the ability of *cisoid* **15** and its *transoid* form (not shown) to undergo H/D exchange was reduced.

Having identified the increased reactivity associated with the enol-form of aryl-derived MAHTs we considered the possibility that under suitable reaction conditions they may participate in a unique *base-* and *metal-free* aldol reaction generating β-hydroxy thioesters similar to (±)-**17** (Scheme 3) derived from the decarboxylation of adducts based on (±)-**16** which have been proposed by Fagnou et al. in using MAHO.[12d]

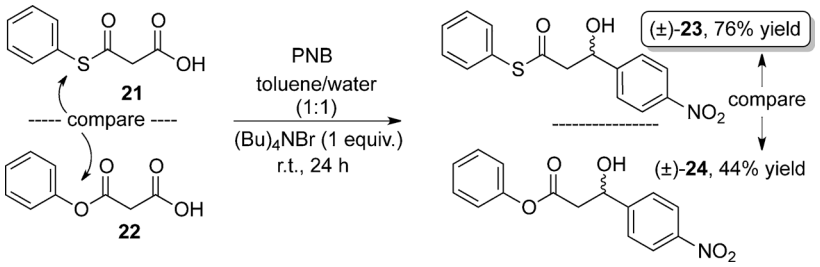
Whilst researching for examples of '*base-free* chemistry' we were intrigued by a report from Maruoka et al. that detailed a phase-transfer conjugate addition reaction between β-nitrostyrene and *rac-N*-Boc-2-phenyloxindole that generated (±)-**19**. Thus in a biphasic toluene/water solvent system, **19** was generated in a 95% yield with tetrabutylammonium bromide (TBAB) and the base potassium carbonate. Alternatively, under *base-free* chiral phase-transfer conditions optically active (*S,S*)-**19** was afforded in a 93% yield in the presence of an enantiomerically enriched biaryl quaternary ammonium salt (see box, Scheme 4). Maruoka et al. proposed in their asymmetric *base-free* process that the optically active bifunctional phase-transfer agent generated an *in situ* 'enolate chiral ion-pair' similar to **20** and this mediated the observed asymmetric Michael reaction affording (*S,S*)-**19**.[13]



Scheme 4. *Base-free* asymmetric conjugate addition reaction between β-nitrostyrene and *rac-N*-Boc-2-phenyloxindole.

Results and Discussion

We pondered on the possibility that by dovetailing the enhanced reactivity associated with aryl thioester-derived MAHTs together with a phase-transfer protocol it might prove viable to generate a unique *base-free, metal-free* aldol reaction. Thus in the context of the aldol chemistry outlined in Scheme 3, we initiated the first preliminary steps towards establishing if thiophenol-derived MAHT (**21**) and phenol-derived MAHO (**22**) or their enol-forms were nucleophilic



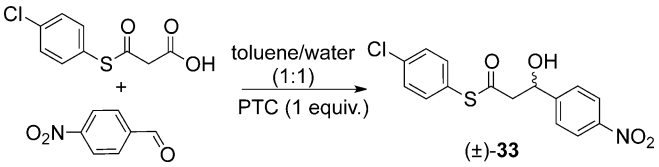
Scheme 5. Comparing the reactivity of MAHT **21** and MAHO **22** with 4-nitrobenzaldehyde under phase-transfer tetrabutylammonium bromide (TBAB) reaction conditions.

enough to react with an electron-poor aldehyde. Choosing 4-nitrobenzaldehyde as a 'model' electrophilic substrate it was combined with Marouka's solvent system (toluene/water) and phase-transfer agent tetrabutylammonium bromide (TBAB). Gratifyingly, both MAHT **21** and MAHO **22** reacted, independently, with 4-nitrobenzaldehyde (PNB). Thus thioester-derived MAHT **21** afforded (±)-3-hydroxy-3-(*para*-nitrophenyl)propanethiolate (±)-**23**, and MAHO **22** returned (±)-phenyl 3-hydroxy-3-(4-nitrophenyl)propanoate (±)-**24** in 76% and 44% yields, respectively (Scheme 5). These preliminary and important results further confirmed our previous findings[8] and established that the *more* reactive MAHT **21** afforded, under essentially identical conditions, a higher yield of the desired thioester aldol adduct (±)-**23** than the corresponding less reactive MAHO.

It was important to ascertain if electron-donating, i.e., 4-CH_3O (**25**) or electron-withdrawing groups, i.e., 4-CF_3O (**26**) were compatible with and not detrimental to the aldol reaction when incorporated on the thiophenyl ring of the MAHT. Gratifyingly both **25** and **26** afforded the desired β-hydroxy thioesters (±)-**30** and (±)-**31** in excellent 84% and 75% yields, respectively. Furthermore, when 4-halophenyl MAHTs were incorporated an interesting halogen effect was observed. Thus 4-bromo, **27**, 4-chloro, **28**, and 4-fluorophenyl derived **29** afforded the desired (±)-β-hydroxy thioesters (±)-**32**–(±)-**34** with *increasing* efficiency, i.e., in 64%, 86% and 96% yields, respectively.

The efficient synthesis of (±)-**33** using toluene, water and cheap 'off the shelf' starting materials afforded us the opportunity to explore the effect of different solvents (Table 1, A–K) on the base-free aldol reaction. Substituting toluene for acetonitrile or ethanol generated completely *homogenous* reaction mixtures; interestingly both afforded (±)-**33** but in reduced 42% and 47% yields, respectively. Incorporating THF a *nearly* homogenous reaction mixture was generated; in this case (±)-**33** was isolated in an *increased* 72% yield. In contrast to toluene, all three reactions also generated unwanted (*E*)-*S*-4-chlorophenyl 3-(4-nitrophenyl)prop-2-enethioate (**35**, Figure 1) in 39%, 40% and 17% yields, respectively. Switching to an essentially completely *biphasic* solvent system the use of ester, aromatic or chlorinated solvent/water combinations afforded (±)-**33** in high purity and improved yields (see Table 1). Chloroform was particularly promising with the 4-nitrobenzaldehyde rapidly consumed and the desired (±)-β-hydroxy thioester (±)-**33** afforded in an excellent 96% yield (see entry K, Table 1). Thus it seemed evident that an important factor for the clean and efficient synthesis of the aldol products was the need for an aqueous biphasic solvent system (*vida infra*). Changing the ratio of chloroform to water from 1:1 to 1:5 had no observable effect on the reaction outcome.

Table 1. Effect of different solvents on the ratio of (±)-**33**, **35** and 4-nitrobenzaldehyde (PNB).



Entry	Solvent	(±)-**33**:**35**:PNB
A	acetonitrile	42:39:19
B	ethanol	47:40:13
C	tetrahydrofuran	72:17:11
D	ethyl acetate	84:4:12
E	hexane	82:2:16
F	xylene	88:5:7
G	ether	87:6:7
H	toluene	89:3:8
I	anisole	92:1:7
J	dichloromethane	88:2:10
K	chloroform	96:0:4

The effect on the yield, efficiency, aldol reaction products and times of employing alternative phase-transfer agents had not yet been investigated. In contrast to homogeneous reactions, the incorporation of a phase-transfer process involves at least one physical phenomenon; the transfer of the reactants between the two phases. As noted by others[14] the role of phase-transfer mediators as perhaps anion 'transport-

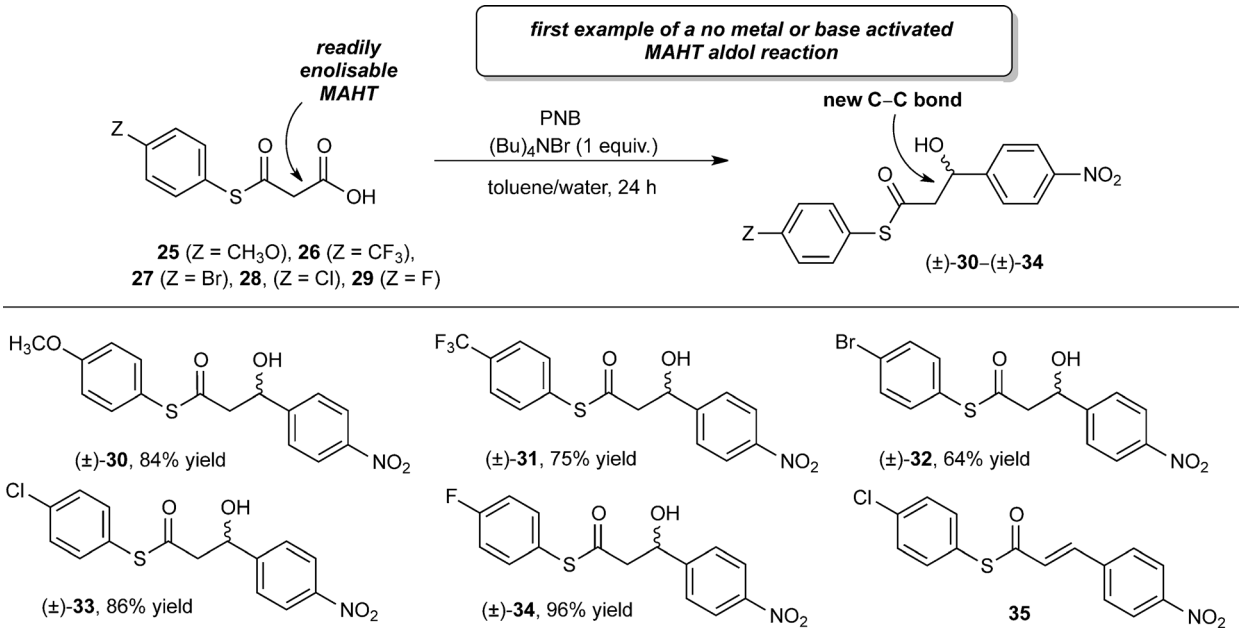
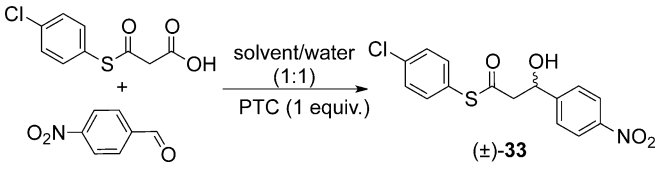


Figure 1. Base-free aldol synthesis of (±)-**30**–(±)-**34**.

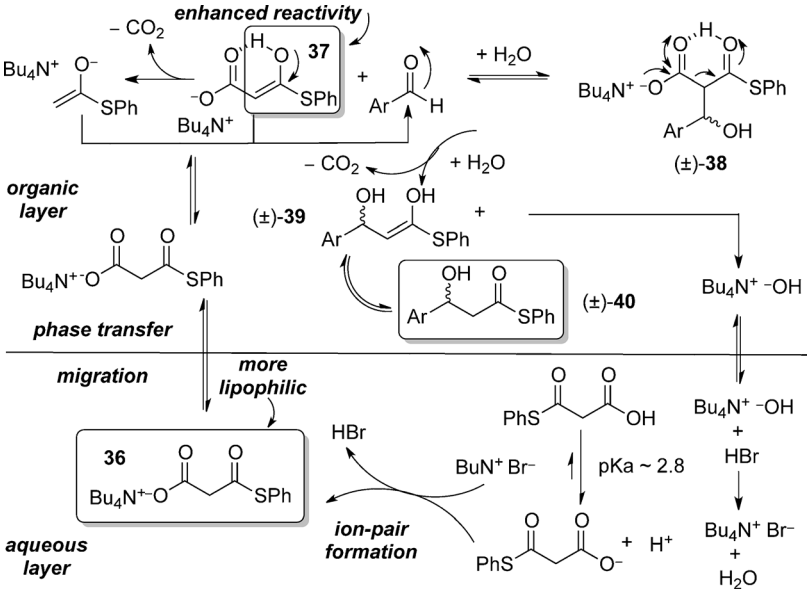
ers' or, potentially, in the formation of non-covalent ion-pairs affords a certain amount of mechanism ambiguity. Thus developing a phase-transfer agent for our previously unknown process is in the first instance a largely empirical process. Exploring the ability of different R_4N^+ salts to mediate the aldol reaction, we started with Me_4NBr (entry L, Table 2). This was a poor reaction with a low conversion rate (a large amount of PNB remained). In contrast, the bulkier tetraheptyl (M) or tetraalkylammonium salts with one long, i.e., tri(methyl)-C_{12}, tri(methyl)-C_{16} or two long aliphatic chains, i.e., di(methyl)-$(C_{18})_2$ afforded (±)-**33** in excellent 82–93% yields (entries L–R, Table 2). Interestingly, albeit it is a different reaction, the efficiency of phenol alkylation[14] is known to be affected by the cationic size and 'length' of the R groups on the tetraalkylammonium salts. Thus when R is methyl, ethyl or *n*-propyl the ammonium salts 'transport' only trace amounts of R_4N^+ phenoxide into the organic layer resulting in poor yields of alkylated phenols.

By analogy in our aldol reaction using tetramethylammonium bromide results in the transfer of only small quantities of the R_4N^+·MAHT ion-pair (**36**, R = Me group, Scheme 6) into the organic layer which limits the potential for an aldol reaction to take place. Denmark et al. and others have established the role and mechanism of PTCs[14] to be complicated by the fact they can operate *via* an 'extraction' or 'interfacial' mechanism depending on the pK_a of the substrate. Carboxylic acid-derived MAHTs, i.e., **21** have pK_{a1} values of ~2.8 and could react either *via* an 'extraction' or 'interfacial mechanism'. A tentative extraction-based mechanism based on the initial formation of a tetrabutylammonium β-carboxylate anion ion-pair, i.e., **36** (R = Bu) in the aqueous layer is outlined in Scheme 6. Due to the enhanced lipophilicity of **36** (relative to TBAB and **11**) it migrates into the organic layer and undergoes thioester-thioenol tautomerization and formation of the more reactive thioenol **37**. Reaction with an aldehyde generates adduct **38** which decarboxylates to **39** and now undergoes thioenol-thioester tautomerization affording the desired (±)-β-hydroxy thioester **40**.[15] A stark difference between the phase-transfer-mediated reactions employing TBAB, TBAC (Q) and TBAI [all afforded (±)-**33**] was the complete lack of reaction with TBAF (not shown in Table 2). Possible reasons are the $(Bu)_4N^+$ and F^- are so tightly associated that generating a $MAHT^-$·$(Bu)_4N^+$ ion-pair (*cf.* **36**) is not possi-

Table 2. Phase-transfer-mediated synthesis of (±)-**33**.



Entry	PTC	(±)-**33**:**35**:PNB
L	$[(CH_3)_4N]Br$	44:13:43
M	$[(C_7H_{15})_4N]Br$	91:1:8
N	$[(CH_3)_3(C_{12}H_{25})N]Br$	82:7:11
O	$[(CH_3)_3(C_{16}H_{33})N]Br$	85:7:8
P	$(CH_3)_2(C_{18}H_{37})_2N]Br$	93:3:4
Q	$[(C_4H_9)_4N]Cl$	88:1:11
R	$[(C_4H_9)N]I$	88:3:9



Scheme 6. Tentative mechanistic rational that may account for the formation of aldol adducts under phase-transfer conditions.

ble, alternatively the water soluble TBAF efficiently solvates the F^- to such an extent that ion-pair formation is repressed and the synthesis of entities based on (±)-**40** inhibited.[16]

It was important to establish the generality of the reaction. A range of different aromatic aldehydes and 3-(4-chlorophenylthio)-3-oxopropanoic acid (**28**) were added to biphasic chloroform/water that contained TBAB. Table 3 outlines the results from this unoptimized study. The yields are good, i.e., >50%, for example, 53% for (±)-**49** to quantitative for (±)-**48**. Furthermore the protocol was tolerant of diverse functionality, i.e., halide, heterocycle, thioether and cyano groups. The increase in yield when 2-→4-chlorobenzaldehydes were incorporated suggests the protocol is tolerant of *ortho*-, *meta*- or *para*-aryl ring substitution. Confirming electron-deficient aldehydes as excellent substrates, pentafluorobenzaldehyde afforded a quantitative yield of (±)-**48** in less than two hours. Also worthy of note is the 63% yield for (±)-**41** which compared to the 22% yield for the previously reported *metal-catalyzed* synthesis of similar (±)-**10** (Scheme 2) represents an encouraging and significant improvement. Confident that our protocol was robust we wanted to ascertain, as our mechanistic overview (Scheme 6) indicates, that water is indeed a critical component for an efficient aldol reaction. Dissolving 3-(4-chlorophenylthio)-3-oxopropanoic acid (**28**), TBAB and 4-nitrobenzaldehyde in anhydrous $CDCl_3$ afforded a *homogeneous* solution.

Table 3. Diverse aldehydes employed and yields returned for the synthesis of β-hydroxy thioesters (±)-**41**–(±)-**54** (see Scheme 6).

(±)-β-Hydroxy thioester/aldehyde	Yield
(±)-**41**, benzaldehyde	63%
(±)-**42**, 2-chlorobenzaldehyde	61%
(±)-**43**, 3-chlorobenzaldehyde	82%
(±)-**44**, 4-chlorobenzaldehyde	93%
(±)-**45**, 2-fluorobenzaldehyde	42%
(±)-**46**, 4-fluorobenzaldehyde	56%
(±)-**47**, 3,4-difluorobenzaldehyde	44%
(±)-**48**, pentafluorobenzaldehyde	100%
(±)-**49**, 3-bromo-4-fluorobenzaldehyde	53%
(±)-**50**, 4-trifluoromethybenzaldehyde	61%
(±)-**51**, 3-trifluoromethybenzaldehyde	82%
(±)-**52**, 4-cyanobenzaldehyde	88%
(±)-**53**, 4-thiobenzaldehyde	56%
(±)-**54**, 2-furaldehyde	84%

Figure 2S outlines the informative components of the ^{1}H NMR spectrum acquired in <5 min. Probing for evidence of a reaction between these or formation of intermediates, additional spectra were acquired over 24 h.

It is clear that on comparing S, T and U (Figure 2) no detectable changes are evident nor are the formation of other by-products in a time frame that previously successful reactions in the *presence* of water afforded excellent yields of (±)-**33**. Injecting an equal volume of anhydrous D_2O *via* the septum generated a *heterogeneous* reaction mixture. A subsequent ^{1}H NMR acquired in less than 5 min after the addition indicated that *significant* changes had occurred within the reaction (see V, Figure 2). Additional spectra were acquired at 6 and 24 h (see W and X). Comparing S–U (*homogeneous*) with V–X (*biphasic*), it is evident that generating a biphasic reaction mixture

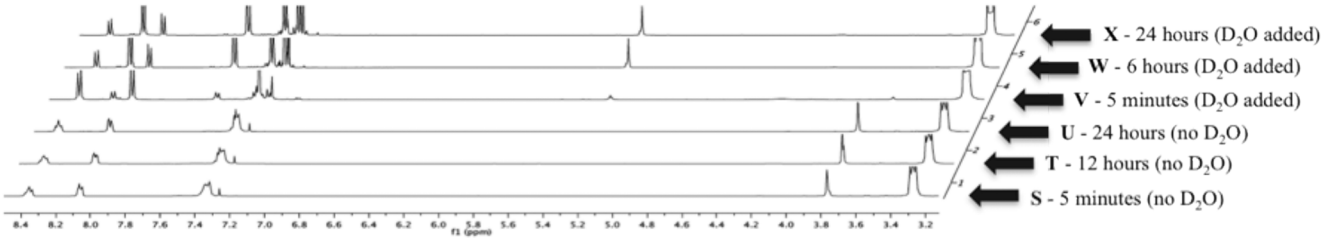
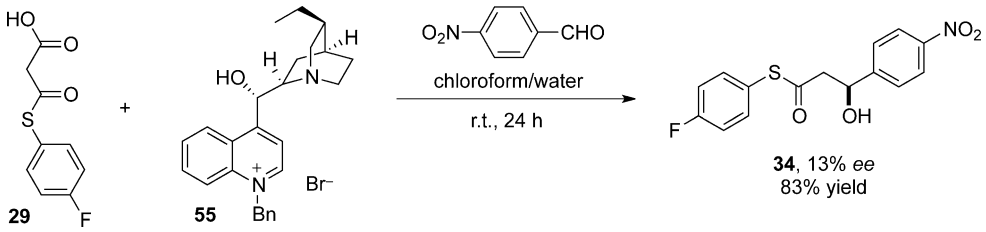


Figure 2. 24 hour ^{1}H NMR experiment indicates the need for water in the TBAT-mediated aldol reaction.

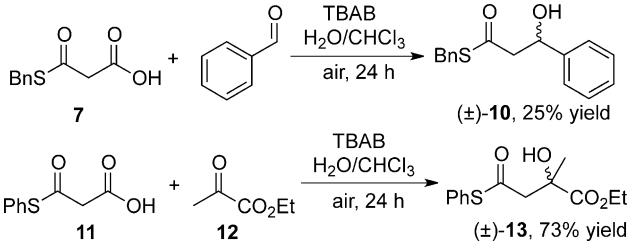


Scheme 7. Asymmetric synthesis of *S*-phenyl 3-(4-fluorophenyl)-3-hydroxypropanethioate **34** using **55**.

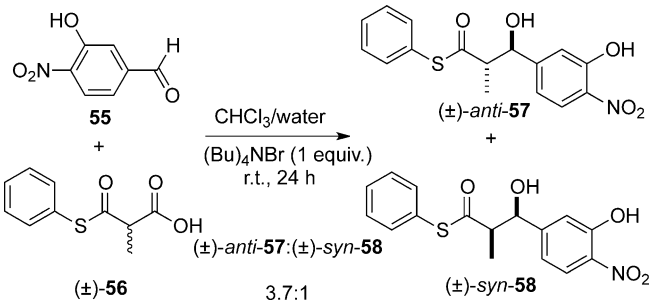
with (H)D_2O is absolutely critical for the efficient consumption of **28**. Relating this to our tentative mechanistic rational (Scheme 6) indicates that formation of ion-pair **36** is very slow in an anhydrous environment. Presumably this can be attributed to the poor dissociation characteristics of **28** in chloroform; the products of which are required for the exchange process with TBAB that results in the formation of an ion-pair, *cf.* **36**. However this situation changes radically when the reaction is transformed into a heterogeneous system, now carboxylic acid **28** migrates into the water and undergoes efficient dissociation. The resulting 3-oxo-3-(phenylthio)propanoate anion undergoes anion exchange with TBAB generating ion-pair **36** which, because of its increased lipophilicity, migrates out of the aqueous layer into the organic phase ($CDCl_3$) where it tautomerizes affording the nucleophilic thioenol **37**. This undergoes an aldol reaction with the electrophilic *para*-nitrobenzaldehyde generating **38**. This decarboxylates to **39** which is followed by a thioenol-thioester tautomerization generating the desired aldol adduct **40** (Scheme 6). It is also possible that **37** undergoes decarboxylation first and generates a tetrabutylammonium thioenol ion pair that subsequently reacts with PNB (Scheme 6) affording (±)-**40** directly.

The asymmetric synthesis of **34** was attempted using the optically active phase-transfer agent *N*-benzyldihydroquinidine bromide **55**, 3-(4-fluorophenylthio)-3-oxopropanoic acid **29**, *para*-nitrobenzaldehyde and our standard, biphasic ambient temperature reaction conditions. Demonstrating the robust nature of our protocol, **34** was afforded in an excellent 83% yield. Encouragingly chiral HPLC analysis confirmed that in addition to an excellent yield **29** was not racemic (13% *ee*). This preliminary, unoptimized and encouraging result suggests that our base- and metal-free aldol reaction is amenable to the asymmetric synthesis of β-hydroxy thioesters. Further studies on the asymmetric synthesis of chiral non-racemic β-hydroxy arylthioesters using quinuclidine salts are currently underway in our laboratory and will be reported in due course. Unfortunately attempted mediation of the reaction outlined in Scheme 7 using catalytic quantities of TBAB or **55** afforded poor yields (<20%) of adducts **34**.

We sought 'like-for-like' comparisons of our *base-free* aldol reaction with a *metal-catalyzed*, and *base-mediated* synthesis of (±)-β-hydroxy thioesters. Initiating this, the copper(II)-mediated synthesis of (±)-**10** in 22% yield[11a] (Scheme 2) reported by Shair et al. was considered an appropriate benchmark against which we could compare our protocol. After generating *S*-benzyl-derived MAHT **7** it was reacted with benzaldehyde and TBAB in 'off the shelf' chloroform and water – no precautions were taken to exclude O_2. Gratifyingly, (±)-**10** (Scheme 8) was afforded in an unoptimized, slightly higher 25% yield which could probably be further improved as we also



Scheme 8. Metal- and base-free aldol synthesis of (±)-**10** and (±)-**13**.



Scheme 9. Probing the diastereoselectivity of a *base- and metal-free* aldol reaction between **55** and (±)-**56** generating (±)-*anti*-**57** and (±)-*syn*-**58**.

isolated 5% of (*E*)-*S*-benzyl 3-phenylprop-2-enethioate [not shown, presumably generated *via* dehydration of (±)-**10**] increasing the overall yield to ~30%.

Comparing our base-free protocol with the Fagnou et al. triethylamine[12d] mediated synthesis of (±)-**13** we again took no precautions to remove O_2 (no inert atmosphere), and employed 'off the shelf' reagents/solvents. Gratifyingly the TBAB-mediated aldol reaction employing *S*-phenyl-derived **11** and ethyl pyruvate afforded (±)-**13** *via* an exceptionally mild, non-basic or metal-containing reaction affording the product in an unoptimized and slightly improved 73% yield (Scheme 8).

Shair et al. outlined the diastereoselectivity of their metal-mediated aldol reaction generating (±)-*syn*-**58** and (±)-*anti*-*S*-phenyl 3-hydroxy-3-(3-hydroxy-4-nitrophenyl)-2-methylpropanethioate **57** from readily synthesized (±)-**56**[17] and aldehyde **55**. Importantly, they assigned *via* ^{1}H NMR the relative diastereoselectivity of the resulting thioesters as (±)-*anti*-**57** and (±)-*syn*-**58**. Thus the copper(II)-catalyzed process afforded (±)-*anti*-**57** and (±)-*syn*-**58** in an 83% yield and 9:1 (*syn*:*anti*) ratio, respectively.[11b] With ease and speed of reaction in mind we also opted to incorporate commercially available 3-hydroxy-4-nitrobenzaldehyde **55** [*cf.* the straighforward and efficient synthesis of (±)-**23**, Scheme 5] in to a diastereoselective reaction using (±)-**56**.

Gratifyingly, our *metal, base-free* protocol afforded (±)-*anti*-**57** and (±)-*syn*-**58** in an unoptimized 49% yield (Scheme 9). Using Shairs' reported ^{1}H NMR data the diastereomeric *syn*-protons at 5.18 and 3.09 were integrated and compared with the *anti*-diastereomeric protons observed at 4.84 and 3.03 ppm. This established a 3.7:1 ratio in favour of (±)-*anti*-**57**, this diastereomeric 'switch' is interesting and important because it suggests that our phase-transfer TBAB-mediated reaction is mechanistically intriguing, unique and complementary to current metal- and base-mediated procedures that afford the opposite *syn*-diastereomers.

Conclusions

It is crucial that innovative, green and sustainable reactions be developed that imitate reactions used by Nature for the biosynthesis of complex natural products. Here we have outlined our preliminary successful efforts towards developing an extremely simple biomimetic inspired approach to C–C bond formation that generates important synthetic and biological building blocks based on β-hydroxy thioesters. Exploiting the enhanced reactivity associated with a series of *N*-aryl malonic acid half thioesters (MAHTs) we have established their potential to undergo an efficient base- and metal-free aldol reaction with a series of structurally and functionally diverse aldehydes. Furthermore we have established that our aldol reaction is readily mediated by a variety of > C_3-tetraalkyl ammonium salts but not tetramethylammonium salts and that water and biphasic conditions are critically important.

Employing readily available structurally and functionally diverse aldehydes and easily generated MAHTs we have probed the scope of the reaction and synthesized more than 24 different β-hydroxy thioesters *via* an environmentally benign process (only by-product is CO_2), using cheap 'off the shelf' R_4N^+ salts and mild PTC conditions that do not require oxygen-free or anhydrous solvents.

From a mechanistic point of view it is interesting to note the contrasting *anti*-diastereomeric induction favoured in our biphasic base- and metal-free aldol reaction whilst, albeit it is a different reaction, the use of a metal- or base-mediated processes affords *syn*-diastereomers as the major component. Thus our biphasic activation of MAHTs and their subsequent application in aldol reactions is complementary in scope affording structurally diverse aldol adducts and sits 'side-by-side' in the 'aldol tool box' along with base-, acid- and metal-MAHT 'activation'.

In summary, a simple solution to the need for milder, less harsh reaction conditions that mimic Nature's non-metal biosynthetic activation of MAHTs in fatty acid and polyketide biosynthesis has been developed. We are exploring the enormous synthesis potential of our remarkably mild MAHT/PTC traceless activation protocol within complex molecule and asymmetric synthesis. The results of these studies will be reported in due course.

Experimental Section

General Information

All solvents and reagents were purchased from commercial sources and used as received. Analytical thin-layer chromatography (TLC) was performed on Merck Silica gel 60 F_{254}

plates, with visualization by UV light and/or potassium permanganate stain followed by heating. Flash column chromatography was performed using Davisil 40–63 μm silica gel. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance 500 (500 MHz) spectrometer. Chemical shifts are reported in δ (ppm) and referenced to residual solvent signals (^{1}H NMR: $CDCl_3$ at 7.26 ppm, CD_3CN at 1.94 ppm, CD_3OD at 3.31 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, CD_3CN at 1.32, 118.26 ppm). Signal multiplicities are described as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, p = pentuplet, m = multiplet, br = broad. IR spectra were recorded on a Perkin–Elmer Spectrum 100 spectrometer. MALDI-TOF mass spectra were recorded on a Shimadzu Axima-CFR spectrometer. High resolution mass spectrometry was carried out by the EPSRC National Mass Spectrometry Facility, Swansea, U.K. Melting points were recorded using a Stuart Scientific SMP1 apparatus and are uncorrected. Percentage yield refers to the isolated yield of analytically pure material unless otherwise stated. Synthesis/physicochemical data of **7**,[11d] **11**,[8] **21**,[8] **22**,[8] **23**,[19a,b] **25**–**29**,[8] **35**[18] were similar to those reported in the literature. *ReagentPlus* grade TBAB (Aldrich 99%, catalogue number 193119–100 g) was used. Performing the reaction in toluene/water (1:1) without TBAB or in either pure water of anhydrous toluene afforded no reaction products.

General Procedure for Base-Free PTC Decarboxylative Aldol Reaction

Malonic acid half thioester (1 equivalent) and 4-nitrobenzaldehyde (1 equivalent) were dissolved in an organic solvent. *N,N,N,N*-Tetrabutylammonium bromide (1 equivalent) and distilled water (same volume as the organic solvent) were added. The resulting biphasic mixture was vigorously stirred for 24–48 h (in some cases the mixture was warmed to 40 °C to enhance reaction times). After this time, the mixture was diluted with distilled water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed under vacuum, affording a pale yellow oil. The product was purified by flash column chromatography on silica gel, eluting with dichloromethane/petroleum ether as specified.

Synthesis of *rac*-*S*-4-Methoxyphenyl 3-Hydroxy-3-(4-nitrophenyl)propanethioate (±)-30

Column solvent: dichloromethane (100%); $R_f = 0.21$ (dichloromethane); white solid; yield: 248 mg (0.74 mmol, 84%); mp 130–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.22$ (d, $J = 7.1$ Hz, 2H), 7.56 (d, $J = 7.4$ Hz, 2H), 7.30 (d, $J = 7.1$ Hz, 2H), 6.96 (d, $J = 7.0$ Hz, 2H), 5.30 (t, $J = 6.0$ Hz, 1H), 3.83 (s, 3H), 3.36 (br s, 1H), 3.05 (d, $J = 6.8$ Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 198.6$, 161.2, 149.4, 147.6, 136.2, 126.6, 124.0, 117.2, 115.2, 70.0, 55.5, 51.3; FT-IR (thin film): $\nu = 3511$, 1692, 1519, 1345, 1243, 1026 cm^{-1}; MS (MALDI-TOF): $m/z = 372.14$ [M + K]; HR-MS (HNESP): $m/z = 334.0747$, exact mass calculated for $C_{16}H_{16}NO_5S$ $[M+H]^+$: 334.0744.

Synthesis of *rac*-*S*-4-Trifluoromethylphenyl 3-Hydroxy-3-(4-nitrophenyl)propanethioate (±)-31

Column solvent: dichloromethane (100%); $R_f = 0.34$; white solid; yield: 211 mg (0.57 mmol, 75%); mp 98–100 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.24$ (d, $J = 8.8$ Hz, 2H), 7.70 (d, $J = 6.0$ Hz, 2H), 7.58 (d, $J = 8.6$ Hz, 2H), 7.54 (d, $J = 7.2$ Hz, 2H), 5.38–5.33 (m, 1H), 3.18–3.06 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 195.6$, 149.2, 147.7, 134.7, 132.0 (q, $J = 33.3$ Hz), 131.3, 126.7, 126.3 (q, $J = 3.9$ Hz), 124.1, 123.8 (q, $J = 272.5$ Hz), 69.9, 52.0; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta = -62.9$; FT-IR (thin film): $\nu = 3424$ (OH), 1699 (C=O), 1520 ($C=C_{arom}$), 1348, 1324 (C-N), 1169, 1128 (C-F), 1065 cm^{-1} (C-O); MS (MALDI-TOF): $m/z = 409.18$ [M + K]; HR-MS (ASAP): $m/z = 389.0785$, exact mass calculated for $C_{16}H_{16}F_3N_2O_4S$ $[M+NH_4]^+$: 389.0777.

Synthesis of *rac*-*S*-4-Bromophenyl 3-Hydroxy-3-(4-nitrophenyl)propanethioate (±)-32

Following the general procedure outlined above (±)-**32** was generated as a white solid; yield: 189 mg (0.49 mmol, 64%). Purification of (±)-**32** was *via* silica gel chromatography using dichloromethane (100%, $R_f = 0.40$). (±)-**32** had the following physicochemical properties: mp 110–111 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.23$ (d, $J = 8.7$ Hz, 2H), 7.56 (d, $J = 8.4$ Hz, 4H), 7.26 (d, $J = 8.4$ Hz, 2H), 5.32 (dd, $J = 7.9$, 4.5 Hz, 1H), 3.11–3.05 (m, 2H), 2.54 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 196.4$, 149.3, 147.7, 136.0, 132.8, 126.7, 125.7, 124.8, 124.0, 69.9, 51.8; FT-IR (thin film): $\nu = 3495$, 3088, 2920, 1684, 1607, 1516, 1472, 1343, 1066 cm^{-1}; MS (MALDI-TOF): $m/z = 381.23$; HR-MS (HASP): $m/z = 381.9736$, calculated for $C_{15}H_{13}BrNO_4S$ $[M+H]^+$: 381.9743.

Synthesis of *rac*-*S*-4-Chlorophenyl 3-Hydroxy-3-(4-nitrophenyl)propanethioate (±)-33

Following the general procedure outlined above (±)-**33** was generated as a white solid; yield: 252 mg (0.75 mmol, 86%). Purification of (±)-**33** was *via* silica gel chromatography using dichloromethane/petroleum ether (6:4, $R_f = 0.16$). Physicochemical data for (±)-**33** are: mp 94–96 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.23$ (d, $J = 8.8$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.42 (d, $J = 8.6$ Hz, 2H), 7.33 (d, $J = 8.6$ Hz, 2H), 5.35–5.31 (m, 1H), 3.18 (br s, 1H), 3.13–3.03 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 196.6$, 149.2, 147.7, 136.6, 135.8, 129.8, 126.7, 125.0, 124.0, 69.9, 51.8; FT-IR (thin film): $\nu = 3415$, 1704, 1505, 1477, 1145, 1013 cm^{-1}; MS (MALDI-TOF): $m/z = 360.09$ [M + Na]; HR-MS (ASAP): $m/z = 338.0243$, calculated for $C_{15}H_{13}ClNO_4S$ $[M+H]^+$: 338.0248.

Synthesis of *rac*-*S*-4-Fluorophenyl 3-Hydroxy-3-(4-nitrophenyl)propanethioate (±)-34

Following the general procedure outlined above (±)-**34** was generated as a white solid; yield: 288 mg (0.90 mmol, 96%). Purification and physicochemical data for (±)-**34** are: purified on silica using dichloromethane/petroleum ether (7:3) ($R_f = 0.35$); physicochemical data for (±)-**34**: mp 85–87 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.24$ (d, $J = 8.7$ Hz, 2H), 7.57 (d, $J = 8.5$ Hz, 2H), 7.38 (dd, $J = 8.8$, 5.2 Hz, 2H), 7.14 (t, $J = 8.6$ Hz, 2H), 5.33 (dd, $J = 7.3$, 5.1 Hz, 1H), 3.09 (d, $J = 2.6$ Hz, 1H), 3.07 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta =$

197.1, 163.4 (d, $J=251.2$ Hz), 149.3, 147.6, 136.7 (d, $J=8.6$ Hz), 126.6, 124.0, 121.9 (d, $J=3.5$ Hz), 116.9 (d, $J=22.2$ Hz), 69.9, 51.6; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta=-109.99$; FT-IR (thin film): $\nu=3504$ (OH), 1698 (C=O), 1591–1519 (C=C aromatic), 1347 (C-F), 1491–1227 (C-NO_2), 1068 cm^{-1} (C-O alcohol); MS (MALDI-TOF): $m/z=344.10$ [M+Na]; HR-MS (ASAP): $m/z=322.0537$, calculated for $C_{15}H_{13}FNO_4S$ $[M+H]^+$: 322.0544.

Synthesis of *rac*-*S*-Phenyl 3-Hydroxy-3-(4-nitrophenyl)propanethioate (±)-41

Following the general procedure outlined above (±)-**41** was generated as a white solid. Physicochemical data for (±)-**41**, a known compound, are as reported in the literature.[19] Column: dichloromethane (100%) $R_f=0.44$; yield: 160 mg (0.55 mmol, 63%); mp 104–106 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.37$–7.22 (m, 9H), 5.15 (d, $J=9.0$ Hz, 1H), 3.06 (dd, $J=16.0$, 9.1 Hz, 1H), 2.96 (dd, $J=16.0$, 3.4 Hz, 1H), 2.77 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=196.6$, 142.2, 136.3, 135.8, 129.7, 128.8, 128.2, 125.8, 125.6, 70.9, 52.4; FT-IR (thin film): $\nu=3507$ (OH), 1685 (C=O), 1387, 1045 cm^{-1} (C-O alcohol); HR-MS (HNESP): $m/z=293.0401$, calculated for $C_{15}H_{14}ClO_2S$ $[M+H]^+$: 293.0398.

Synthesis of *rac*-*S*-4-Chlorophenyl 3-(2-Chlorophenyl)-3-hydroxypropanethioate (±)-42

Following the general procedure outlined above (±)-**42** was generated as a white solid; yield: 173 mg (0.53 mmol, 61%). Purification of (±)-**42** was *via* silica gel chromatography using dichloromethane/petroleum ether (8:2, $R_f=0.29$). Physicochemical data for (±)-**42** are: mp 93–95 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.41$ (d, $J=8.5$ Hz, 2H), 7.37–7.31 (m, 6H), 5.20 (dd, $J=8.9$, 3.3 Hz, 1H), 3.08 (dd, $J=16.1$, 8.9 Hz, 1H), 3.01 (dd, $J=16.1$, 3.5 Hz, 1H), 2.94 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=196.7$, 140.6, 136.4, 135.8, 133.9, 129.8, 129.0, 127.2, 125.4, 70.2, 52.1; FT-IR (thin film): $\nu=1698$ (C=O), 1493 (Ar), 1477 (Ar), 1265 cm^{-1} (C-O); MS (MALDI-TOF): $m/z=365.06$ [M+K]; HR-MS (HNESP): $m/z=674.9760$, calculated for $(C_{15}H_{12}Cl_2O_2S)_2Na$ $[2M+Na]^+$: 674.9762.

Synthesis of *rac*-*S*-4-Chlorophenyl 3-(3-Chlorophenyl)-3-hydroxypropanethioate (±)-43

Following the general procedure outlined above (±)-**43** was generated as a white solid; yield: 233 mg (0.71 mmol, 82%). Purification of (±)-**43** was *via* silica gel chromatography using dichloromethane/petroleum ether (8:2, $R_f=0.19$). Physicochemical data for (±)-**43** are: mp 60–62 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.33$–7.29 (m, 3H), 7.26–7.12 (m, 5H), 5.09 (dd, $J=9.0$, 3.5 Hz, 1H), 3.02 (br s, 1H), 2.99 (dd, $J=16.0$, 9.0 Hz, 1H), 2.91 (dd, $J=16.1$, 3.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=196.6$, 144.2, 136.3, 135.8, 134.7, 130.1, 129.7, 128.2, 126.0, 125.3, 123.9, 70.1, 52.1; FT-IR (thin film): $\nu=3584$ (OH), 1699 (C=O), 1391 (Ar), 1421 (Ar), 1265 cm^{-1} (C-O); MS (MALDI-TOF): $m/z=349.08$ [M+Na]; HR-MS (HNESP): $m/z=348.9831$, calculated for $C_{15}H_{12}Cl_2O_2SNa$ $[M+Na]^+$: 348.9827.

Synthesis of *rac*-*S*-4-Chlorophenyl 3-(4-Chlorophenyl)-3-hydroxypropanethioate (±)-44

Following the general procedure outlined above (±)-**44** was generated as a colourless oil; yield: 264 mg (0.81 mmol, 93%). Purification of (±)-**44** was *via* silica gel chromatography using dichloromethane/petroleum ether (1:1, $R_f=0.23$). Physicochemical data for (±)-**44** are: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.63$ (dd, $J=7.7$, 1.6 Hz, 1H), 7.41 (d, $J=8.5$ Hz, 2H), 7.37–7.33 (m, 4H), 7.25 (t, $J=7.6$ Hz, 1H), 5.58 (d, $J=9.3$ Hz, 1H), 3.20 (dd, $J=16.2$, 2.5 Hz, 1H), 3.13 (br s, 1H), 2.95 (dd, $J=16.2$, 9.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=197.0$, 139.5, 136.3, 135.9, 131.4, 129.7, 129.6, 129.1, 127.4, 127.2, 125.5, 67.6, 50.3; FT-IR (thin film): $\nu=3582$ (OH), 1698 (C=O), 1265 cm^{-1} (C-O); MS (MALDI-TOF): $m/z=365.06$ [M+K]; HR-MS (HNESP): $m/z=327.0012$, calculated for $C_{15}H_{13}Cl_2O_2S$ $[M+H]^+$: 327.0008.

Synthesis of *rac*-*S*-4-Chlorophenyl 3-(2-Fluorophenyl)-3-hydroxypropanethioate (±)-45

Following the general procedure outlined above (±)-**45** was generated as a white solid; yield: 113 mg (0.36 mmol, 42%). Purification of (±)-**45** was *via* silica gel chromatography using dichloromethane/petroleum ether (8:2), $R_f=0.28$. Physicochemical data for (±)-**45** are: mp 69–71 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.53$ (td, $J=7.5$, 1.4 Hz, 1H), 7.40 (d, $J=8.5$ Hz, 2H), 7.33 (d, $J=8.5$ Hz, 2H), 7.32–7.27 (m, 1H), 7.18 (td, $J=7.6$, 1.2 Hz, 1H), 7.05 (ddd, $J=10.6$, 8.2, 1.2 Hz, 1H), 5.50 (dd, $J=8.4$, 3.7 Hz, 1H), 3.14 (dd, $J=16.2$, 3.7 Hz, 1H), 3.09 (dd, $J=16.2$, 8.5 Hz, 1H), 3.02 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=196.6$, 159.4 (d, $J=245.8$ Hz), 136.2, 135.8, 129.6, 129.4 (d, $J=8.2$ Hz), 129.1 (d, $J=13.1$ Hz), 127.3 (d, $J=4.2$ Hz), 125.4, 124.5 (d, $J=3.4$ Hz), 115.4 (d, $J=21.3$ Hz), 65.0 (d, $J=2.7$ Hz), 50.7; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta=-118.9$; FT-IR (thin film): $\nu=3419$ (OH), 1705 (C=O), 1586 (C=C aromatic), 1575 (C=C aromatic), 1390 (C-F), 1013 cm^{-1} (C-O alcohol); MS (MALDI-TOF): $m/z=311.34$ [M+H]; HR-MS (ASAP): $m/z=311.0300$, exact mass calculated for $C_{15}H_{13}ClFO_2S$ $[M+H]^+$: 311.0303.

Synthesis of *rac*-*S*-4-Chlorophenyl 3-(4-Fluorophenyl)-3-hydroxypropanethioate (±)-46

Following the general procedure outlined above (±)-**46** was generated as a white solid; yield: 151 mg (0.49 mmol, 56%). Purification of (±)-**46** was *via* silica gel chromatography using 100% dichloromethane ($R_f=0.53$). Physicochemical data for (±)-**46** are: mp 76–78 °C, ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.41$ (d, $J=8.5$ Hz, 2H), 7.38–7.30 (m, 4H), 7.06 (t, $J=8.6$ Hz, 2H), 5.20 (dd, $J=8.8$, 2.8 Hz, 1H), 3.10 (dd, $J=16.0$, 9.0 Hz, 1H), 3.01 (dd, $J=16.1$, 3.5 Hz, 1H), 2.91 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=196.6$, 162.4 (d, $J=246.3$ Hz), 137.8 (d, $J=3.1$ Hz), 136.3, 135.7, 129.6, 127.4 (d, $J=8.1$ Hz), 125.3, 115.6 (d, $J=21.5$ Hz), 70.1, 52.2; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta=-114.1$; FT-IR (thin film): $\nu=1700$ (C=O), 1477 (Ar), 1510 (Ar), 1263 (C-O), 1013.62 cm^{-1} (C-F); MS (MALDI-TOF): $m/z=333.26$ [M+Na]; HR-MS (HNESP): $m/z=333.0126$, calculated for $C_{15}H_{12}ClFO_2SNa$ $[M+Na]^+$: 333.0123.

Synthesis of *rac*-*S*-4-Chlorophenyl 3-(3,4-Difluorophenyl)-3-hydroxypropanethioate (±)-47

Following the general procedure outlined above (±)-**47** was generated as a white solid; yield: 125 mg (0.38 mmol, 44%). Purification of (±)-**47** was *via* silica gel chromatography using 100% dichloromethane, $R_f = 0.42$. Physicochemical data for (±)-**47** are: mp 78–80 °C; ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.34$ (d, $J = 8.5$ Hz, 2H), 7.27 (d, $J = 8.5$ Hz, 2H), 7.25–7.19 (m, 1H), 7.18–7.05 (m, 2H), 5.07–5.02 (m, 1H), 4.54 (s, 1H, OH), 2.98 (dd, $J = 15.1$, 8.5 Hz, 1H), 2.90 (dd, $J = 15.0$, 4.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta =$ 196.6, 151.3 (dd, $J = 246.7$, 69.0, 12.7 Hz), 149.3 (dd, $J =$ 246.7, 69.0, 12.7 Hz), 139.2, 136.4, 135.8, 129.8, 121.7 (dd, $J =$ 6.4, 3.6 Hz), 117.5 (d, $J = 17.3$ Hz), 115.0 (d, $J = 18.0$ Hz), 69.7, 52.0; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta = -136.8$ (d, $J =$ 21.1 Hz), −138.7 (d, $J = 21.2$ Hz); FT-IR (thin film): $\nu =$ 3460, 1698, 1520, 1478, 1014 cm^{-1}; MS (MALDI-TOF): *m/z* = 350.94 [M+Na]; HR-MS (HNESP): *m/z* = 351.0029, exact mass calculated for $C_{15}H_{11}ClFO_2SNa$ $[M+Na]^+$: 351.0029.

Synthesis of *rac*-*S*-4-Chlorophenyl 3-(Pentafluorophenyl)-3-hydroxypropanethioate (±)-48

Following the general procedure outlined above (±)-**48** was generated as a white solid; yield: 331 mg (0.87 mmol, 100%). Purification of (±)-**48** was *via* silica gel chromatography using dichloromethane/petroleum ether (8:2) $R_f = 0.42$. Physicochemical data for (±)-**48** are: mp 110–112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.41$ (d, $J = 8.6$ Hz, 1H), 7.34 (d, $J = 8.6$ Hz, 1H), 5.62–5.57 (m, 1H), 3.49 (dd, $J =$ 16.3, 9.0 Hz, 1H), 3.11 (dd, $J = 16.3$, 4.3 Hz, 1H), 2.97 (d, $J =$ 5.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 195.5$, 146.3–145.8 (m), 144.4–143.8 (m), 142.7–140.0 (m), 139.1–138.5 (m), 137.1–136.7 (m), 136.6, 135.8, 129.8, 125.0, 114.8 (t, $J =$ 17.4 Hz), 62.4, 48.9; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta = -142.4$ to −142.5 (m, 2F), −153.5 (t, $J = 21.0$ Hz, 1F), −161.0 to −161.2 (m, 2F); FT-IR (thin film): $\nu = 3507$ (OH), 1694 (C=O), 1499 (Ar), 1068 (C-O alcohol), 1000 cm^{-1} (C-F); MS (MALDI-TOF): *m/z* = 405.14 [M+Na]; HR-MS (HNESP): *m/z* 404.9748, calculated for $C_{15}H_8ClF_5O_2SNa$ $[M+Na]^+$: 404.9746.

Synthesis of *rac*-*S*-4-Chlorophenyl 3-(3-Bromo-4-fluorophenyl)-3-hydroxypropanethioate (±)-49

Following the general procedure outlined above (±)-**49** was generated as a pale yellow solid; yield: 179 mg (0.46 mmol, 53%). Purification of (±)-**49** was *via* silica gel chromatography using dichloromethane/petroleum ether (8:2) $R_f = 0.24$. Physicochemical data for (±)-**49** are: mp 67 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.52$ (d, $J = 6.6$ Hz, 1H), 7.33 (d, $J =$ 8.4 Hz, 2H), 7.25 (d, $J = 8.5$ Hz, 2H), 7.22–7.19 (m, 1H), 7.04 (t, $J = 8.3$ Hz, 1H), 5.09 (dd, $J = 8.9$, 3.5 Hz, 1H), 2.99 (dd, $J = 16.2$, 8.7 Hz, 1H), 2.92 (dd, $J = 15.9$, 3.6 Hz, 1H), 2.81 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 196.6$, 158.7 (d, $J = 247.8$ Hz), 139.6 (d, $J = 3.7$ Hz), 136.5, 135.8, 131.0, 129.8, 126.4 (d, $J = 7.3$ Hz), 125.2, 116.7 (d, $J =$ 22.4 Hz), 109.4 (d, $J = 21.1$ Hz), 69.6, 52.1; ^{19}F NMR ($CDCl_3$): $\delta = -108.3$; FT-IR (thin film): $\nu = 3465$, 2912, 1694, 1497, 1391, 1248, 1013 cm^{-1}; MS (MALDI-TOF): *m/z* = 429.09 [M+K]; HR-MS (ASAP): *m/z* = 405.9679, exact mass calculated for $C_{15}H_{15}BrClFO_2SN$ $[M+NH_4]^+$: 405.9674.

Synthesis of *rac*-*S*-4-Chlorophenyl 3-(4-Trifluoromethylphenyl)-3-hydroxypropanethioate (±)-50

Following the general procedure outlined above (±)-**50** was generated as a pale yellow solid; yield: 191 mg (0.53 mmol, 61%). Purification of (±)-**50** was *via* silica gel chromatography using 100% dichloromethane, $R_f = 0.48$. Physicochemical data for (±)-**50** are: mp 92–94 °C; ^{1}H NMR (500 MHz, CD_3CN): $\delta = 7.68$ (d, $J = 8.0$ Hz, 2H), 7.58 (d, $J = 8.0$ Hz, 2H), 7.47 (d, $J = 8.5$ Hz, 2H), 7.37 (d, $J = 8.6$ Hz, 2H), 5.22 (dd, $J = 8.4$, 4.5 Hz, 1H), 3.83 (br s, 1H), 3.09 (dd, $J = 15.2$, 8.7 Hz, 1H), 3.02 (dd, $J = 15.3$, 4.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 196.7$, 146.1, 136.4, 135.8, 130.3 (q, $J = 32.4$ Hz), 129.8, 126.1, 125.7 (q, $J = 3.7$ Hz), 125.2, 124.1 (q, $J = 272.0$ Hz), 70.2, 52.0; ^{19}F NMR (471 MHz, CD_3CN): $\delta = -62.9$; FT-IR (thin film): $\nu = 3508$, 2931, 1681, 1480, 1319, 1142, 1048 cm^{-1}; MS (MALDI-TOF): *m/z* = 360.21; HR-MS (ASAP): *m/z* = 361.0276, exact mass calculated for $C_{16}H_{13}ClF_3O_2S$ $[M+H]^+$: 361.0271.

Synthesis of *rac*-*S*-4-Chlorophenyl 3-(3-Trifluoromethylphenyl)-3-hydroxypropanethioate (±)-51

Following the general procedure outlined above (±)-**51** was generated as a colourless oil; yield: 257 mg (0.71 mmol, 82%). Purification of (±)-**51** was *via* silica gel chromatography using dichloromethane/petroleum ether (8:2), $R_f = 0.54$. Physicochemical data for (±)-**51** are: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.67$ (s, 1H), 7.57 (d, $J = 7.9$ Hz, 2H), 7.52–7.48 (m, 1H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 8.3$ Hz, 2H), 5.28 (dd, $J = 8.9$, 3.5 Hz, 1H), 3.11 (dd, $J = 16.1$, 8.9 Hz, 1H), 3.05 (dd, $J = 16.2$, 3.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 196.7$, 143.1, 136.5, 135.8, 131.2 (q, $J = 32.5$ Hz), 129.8, 129.5 (q, $J = 266$ Hz), 129.3, 129.2, 125.3, 125.0 (q, $J =$ 3.6 Hz), 122.7 (q, $J = 3.6$ Hz), 70.2, 52.1; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta = -62.6$; FT-IR (thin film): $\nu = 3440$ (OH), 1694 (C=O), 1478, 1329, 1126 cm^{-1}; MS (MALDI-TOF): *m/z* = 382.97 [M+Na]; HR-MS (HNESP): *m/z* = 361.0276, exact mass calculated for $C_{16}H_{13}ClF_3O_2S$ $[M+H]^+$: 361.0271.

Synthesis of *rac*-*S*-4-Chlorophenyl 3-(4-Cyanomethylphenyl)-3-hydroxypropanethioate (±)-52

Following the general procedure outlined above (±)-**52** was generated as a white solid; yield: 242 mg (0.76 mmol, 88%). Purification of (±)-**52** was *via* silica gel chromatography using dichloromethane/petroleum ether (6:4) $R_f = 0.16$. Physicochemical data for (±)-**52** are: mp 107–109 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.66$ (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 8.1$ Hz, 2H), 7.41 (d, $J = 8.5$ Hz, 2H), 7.32 (d, $J =$ 8.5 Hz, 2H), 5.31–5.23 (m, 1H), 3.15 (br s, 1H), 3.12–2.99 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 196.5$, 147.4, 136.5, 135.8, 132.6, 129.8, 126.5, 125.1, 118.7, 111.9, 70.1, 51.8; FT-IR (thin film): $\nu = 3508$ (OH), 1694 (C=O), 1450 (Ar), 1523 (Ar), 999 cm^{-1} (C-O); MS (MALDI-TOF): *m/z* = 340.0 [M+Na]; HR-MS (HNESP): *m/z* = 318.0347, exact mass calculated for $C_{16}H_{13}ClNO_2S$ $[M+H]^+$: 318.0350.

Synthesis of *rac*-*S*-4-Chlorophenyl 3-(4-Thiomethylphenyl)-3-hydroxypropanethioate (±)-53

Following the general procedure outlined above (±)-**53** was generated as a white solid; yield: 165 mg (0.49 mmol, 56%). Purification of (±)-**53** was *via* silica gel chromatography using dichloromethane/petroleum ether (8:2) $R_f = 0.36$. Physicochemical data for (±)-**53** are: mp 131–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.40$ (d, $J = 8.5$ Hz, 2H), 7.33 (d, $J = 8.5$ Hz, 2H), 7.30 (d, $J = 8.3$ Hz, 2H), 7.25 (d, $J = 8.5$ Hz, 2H), 5.18 (dt, $J = 9.0$, 3.2 Hz, 1H), 3.10 (dd, $J = 16.0$, 9.1 Hz, 1H), 3.00 (dd, $J = 16.0$, 3.5 Hz, 1H), 2.85 (d, $J = 3.3$ Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta =$ 196.6, 139.0, 138.5, 136.3, 135.8, 129.7, 126.8, 126.3, 125.5, 70.5, 52.2, 16.0; FT-IR (thin film): $\nu = 3493$ (OH), 1681 (C=O), 1474 (Ar), 1388 (Ar), 1261 (C-H), 1049 cm^{-1} (C-O); MS (MALDI-TOF): $m/z = 361.07$ [M+Na]; HR-MS (HNESP): $m/z = 361.0097$, calculated for $C_{16}H_{15}ClO_2S_2Na$ $[M+H]^+$: 361.0094.

Synthesis of (±)-*S*-4-Chlorophenyl 3-(Furan-2-yl)-3-hydroxypropanethioate (±)-54

Following the general procedure outlined above (±)-**54** was generated as a white solid; yield: 206 mg (0.73 mmol, 84%). Purification of (±)-**54** was *via* silica gel chromatography using dichloromethane/petroleum ether (8:2), $R_f = 0.31$. Physicochemical data for (±)-**54** are: mp 45–47 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.41$–7.38 (m, 3H), 7.33 (d, $J = 8.5$ Hz, 2H), 6.36–6.33 (m, 1H), 6.30 (d, $J = 3.3$ Hz, 1H), 5.22 (dd, $J = 8.5$, 3.9 Hz, 1H), 3.27 (dd, $J = 16.1$, 8.6 Hz, 1H), 3.16 (ddd, $J = 16.0$, 3.9, 1.4 Hz, 1H), 2.86 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 196.1$, 154.3, 142.5, 136.3, 135.8, 129.7, 125.5, 110.5, 106.8, 64.6, 48.7; FT-IR (thin film): $\nu = 3416$ (OH), 1705 (C=O), 1506, 1477, 1266, 1146, 1013 cm^{-1}; MS (MALDI-TOF): $m/z = 304.99$ [M+Na]; HR-MS (ASAP): $m/z = 300.0449$, exact mass calculated for $C_{13}H_{15}ClO_3SN$ $[M+NH_4]^+$: 300.0456.

Synthesis of (±)-*S*-Benzyl 3-Hydroxy-3-phenylpropanethioate (±)-10

Following the general procedure outlined above (±)-**10** was generated as a colourless oil; yield: 65 mg (0.24 mmol, 25%). Purification of (±)-**10** was *via* silica gel chromatography using petroleum ether/ethyl acetate (10%); $R_f = 0.26$. Physicochemical data for (±)-**10**, a known compound, as reported in the literature:[20] ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.38–7.24 (m, 10H), 5.21 (dt, $J = 9.1$, 3.2 Hz, 1H), 4.22–4.12 (m, 2H), 3.03 (dd, $J = 15.8$, 9.2 Hz, 1H), 2.98 (d, $J = 3.3$ Hz, 1H), 2.95 (dd, $J = 15.8$, 3.4 Hz, 1H); FT-IR (thin film): $\nu =$ 3456, 3030, 2916, 1684, 1492, 1453, 1058 cm^{-1}.

Synthesis of Ethyl 2-Hydroxy-2-methyl-4-oxo-4-(phenylthio)butanoate (±)-13

Following the general procedure outlined above (±)-**13** was generated as a colourless oil; yield: 199 mg (0.74 mmol, 73%). Purification of (±)-**10** was *via* silica gel chromatography using petroleum ether/ethyl acetate (8:2); $R_f = 0.36$. Physicochemical data for (±)-**13**, a known compound, as reported in the literature:[12f] ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.40 (br s, 5H), 4.29–4.20 (m, 2H), 3.65 (s, 1H), 3.27 (d, $J =$ 16.1 Hz, 1H), 3.05 (d, $J = 16.1$ Hz, 1H), 1.45 (s, 3H), 1.28 (t, $J = 7.1$ Hz, 3H); FT-IR (thin film): $\nu = 3499$, 2987, 2932, 1727, 1476, 1445, 1210, 1112, 1011 cm^{-1}.

Synthesis of (±)-2-Methyl-3-oxo-3-(phenylthio)-propanoic acid (±)-56

Employing a slightly different procedure to the literature protocol,[21] methylmalonyl chloride half ester (0.6 g, 4.39 mmol) and thiophenol (0.161 g, 1.47 mmol) were dissolved in anhydrous acetonitrile (5 mL). Triflic acid (0.013 mL, 0.146 mmol) was added *via* syringe and the solution heated to reflux for 3 h under nitrogen. After cooling to room temperature, the solvents and volatiles were removed under vacuum and the impure residue redissolved in dichloromethane and washed with distilled water (3×20 mL). The organic solution was dried over magnesium sulfate and the solvent removed to afford an impure product which was purified *via* flash column chromatography (petroleum ether/ethyl acetate 20–30%). The desired product was obtained as a colourless oil; yield: 0.090 g (0.43 mmol, 29%). Physicochemical data for **56**, a known compound, are as reported in the literature.[3]

Synthesis of *anti*-(2*R*,3*R*)-*S*-Phenyl 3-Hydroxy-2-methyl-3-(3-methyl-4-nitrophenyl)propanethioate (±)-*anti*-57 and *syn*-(2*S*,3*R*)-*S*-Phenyl 3-Hydroxy-2-methyl-3-(3-methyl-4-nitrophenyl)propanethioate (±)-*syn*-58

MAHT (±)-**36** (0.090 g, 0.428 mmol) and 4-nitro-3-hydroxybenzaldehyde (**37**) (0.078 g, 0.428 mmol) were dissolved in chloroform (2 mL). Tetrabutylammonium bromide (0.138 g, 0.428 mmol) and distilled water (2 mL) were added and the mixture stirred vigorously at 40 °C for 24 h. The mixture was diluted with chloroform (101 mL) and water (10 mL) and the aqueous layer extracted with chloroform (3×15 mL). The organic solution was dried over magnesium sulfate, filtered and the solvent removed to afford a crude product which was purified by column chromatography on silica gel (dichloromethane 100% $R_f = 0.26$); to afford the desired *syn* and *anti* compounds (*syn*:*anti* ratio = 1:3.7) as a yellow solid; yield: 70 mg (0.21 mmol, 49%). Physiochemical data for (±)-s*yn*-**58** and (±)-*anti*-**57** matched those previously reported.[6] MS (MALDI-TOF): $m/z = 356.14$, calculated for $C_{16}H_{15}NNaO_5S$ $[M+Na]^+$: 356.06.

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