Synergistic organocatalysis: highly enantioselective desymmetrisation with concomitant *sec*-thiol kinetic resolution

Aldo Peschiulli, Barbara Procuranti, Cornelius J. O'Connor and Stephen J. Connon*

Centre for Synthesis and Chemical Biology, School of Chemistry, University of Dublin, Trinity College, Dublin 2, Ireland. *e-mail: connons@tcd.ie

Abstract

An organocatalytic process mediated by a single small-molecule catalyst involving the highly enantioselective desymmetrisation of an achiral electrophile while it simultaneously kinetically resolves a racemic nucleophile has been developed which allows the efficient direct acylative kinetic resolution of *sec*-thiol substrates for the first time. The levels of enantioselectivity associated with both processes (which exhibit verifiable synergy) are excellent using a readily accessible cinchona alkaloid-derived organocatalyst at low loadings. The inexpensive achiral glutaric anhydride electrophiles are desymmetrised as the resolution progresses with excellent levels of stereocontrol and can be later cleaved to afford highly enantioenriched products (up to 97% *ee*). The potential synthetic utility of the methodology was demonstrated by the synthesis of a drug precursor antipode in excellent yield and enantioselectivity as a by-product of a process which also resolved a *sec*-thiol substrate with a selectivity of S=226 (*i.e.* both thiol antipodes produced in >95% *ee* at 51% conversion).

One of the most convenient methods for the rapid isolation of enantiopure secondary alcohols is the kinetic resolution (KR) of the corresponding racemic materials *via* enantioselective acylation.[1,2] Initially this was carried out using biological catalysts[3,4] however, in recent years several efficient and selective artificial organocatalysts for these processes have become available.[5,6,7,8,9,10,11,12,13,14] While the KR of alcohols is now a mature and useful technology, perhaps surprisingly no analogous direct methods exist for the highly selective, direct catalytic KR of racemic thiols - despite the importance of thiols and organosulfur compounds in organic chemistry[15,16] and chemical biology.[17,18,19] Baker's yeast has been used to resolve a chiral thiol in the presence of glucose, however the resolved material was isolated in trace amounts only and with low enantioselectivity (40% *ee*).[20] To the best of our knowledge only two other reports have appeared concerning the KR of thiols: Cesti *et al*.[21] and Hult *et al.*[22] have developed indirect methodologies based on lipase-catalysed transesterification of thioesters derived from racemic thiols - under optimal conditions the thiol products can be obtained with high enantioselectivity (up to 95% *ee*), however only three thioester substrates were resolved and the methodology required long reaction times (up to 200 h) and high mass loadings of

the enzyme catalyst. It is noteworthy that attempts to utilise one of the lipases to promote the direct acylative KR of thiols failed to produce enantioenriched products.[22]

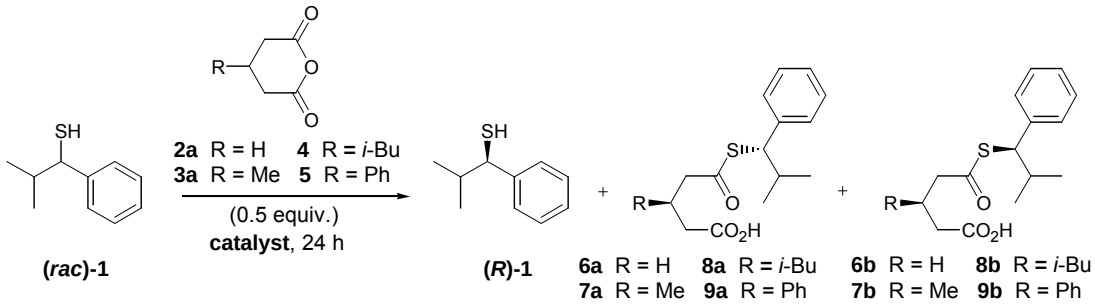
While enantioenriched thiols can be synthesised from the corresponding alcohols, this simply makes one reliant on (and limited by) the availability of the desired alcohol substrate in enantiopure form. In addition – care must be exercised[23] where a substrate (or its derivatives) is capable of racemisation – for instance before this study could begin we required a sample of thiol **1** (Table 1) in enantiopure form so that both enantiomers of **(*rac*)-1** could be unambiguously identified by CSP-HPLC analysis. Thus we took commercially available (*R*)-1-phenyl-2-methyl-propanol (>99% *ee*) and subjected it to a sequence involving mesylation, substitution with thioacetate ion (dry DMSO solvent, rt) and deprotection with $LiAlH_4$, which afforded **(*S*)-1** in a substantially diminished enantiomeric excess of 84.5%, despite considerable care taken to avoid a competing S_N1 substitution pathway. While it was clear to us at the outset that there were particular difficulties associated with the development of an organocatalytic enantioselective acylation protocol for thiol substrates relative to alcohols (*e.g.* 'softer' nucleophile, greater distance between the reacting heteroatom and the stereocentre, and lower heteroatom pK_a), the paucity of methodologies available for the catalytic asymmetric synthesis of enantioenriched thiols – and for the KR of thiols in particular – in the literature encouraged us to focus on the problem.

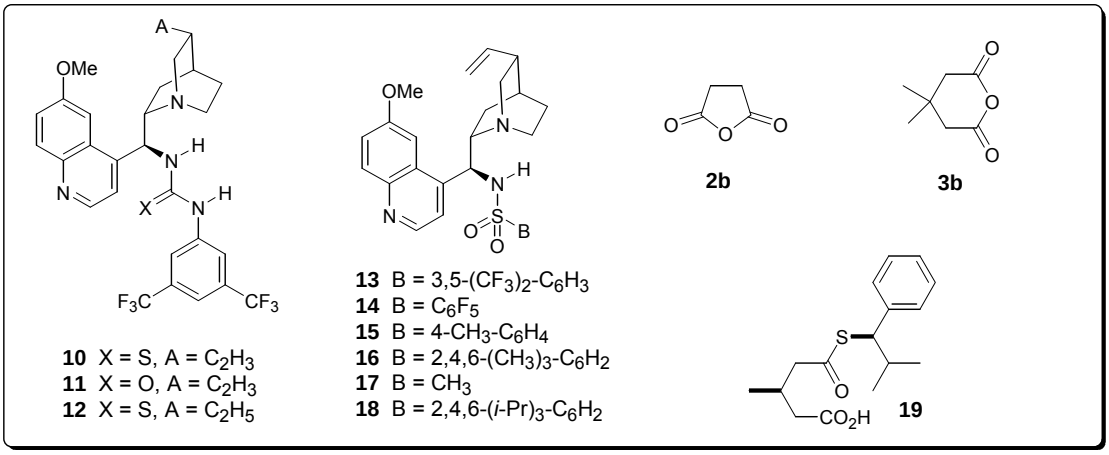
Results and Discussion

Recently, we demonstrated bifunctional thiourea-modified cinchona alkaloid organocatalysts[24] to be capable of catalysing the efficient and selective desymmetrisation of *meso* glutaric anhydrides[25,26,27,28] with achiral alcohol[29] and thiol[30] nucleophiles (a process first reported using artificial catalysts by Nagao *et al*.[31]) at ambient temperature using low catalyst loadings.[32,33] In case of ring opening with thiols, we observed significantly higher enantioselectivity using bulkier, secondary achiral thiols than with primary analogues.[30] This led us to postulate that if catalyst-nucleophile steric interactions play a significant role in determining the efficacy of the desymmetrisation process from a stereoselectivity standpoint, then these putative interactions could potentially also be utilised to discriminate between enantiomers of a racemic chiral thiol nucleophile.

To test this hypothesis, in preliminary experiments we carried out the acylative KR of the racemic *sec*-thiol **1** with glutaric anhydride (**2a**) in the presence of bifunctional (thio)urea-derived organocatalysts **10-12** and sulphonamide **13**, which we[29,30] and Song *et al*.[32,33] respectively have demonstrated to be capable of promoting the addition of achiral alcohols to cyclic anhydrides (Table 1). Initial results were far from encouraging – acylation proceeded smoothly at low catalyst loading (5 mol%), but resulted in products of low enantiomeric excess (entries 1-4). Of the four catalysts tested sulphonamide **13** proved superior to the (thio)urea-derivatives and could promote the KR with a very modest selectivity (k_{fast}/k_{slow})[1] of 1.5 (13% *ee* at 50% conv., entry 4). Further experimentation identified MTBE as the optimal solvent overall, although the KR of **1** was slower but more selective in THF (entries 4-7).

Table 1: Kinetic resolution of thiol 1 with simultaneous desymmetrisation of achiral-anhydrides 3-5





entry	anhydride (equiv.)	catalyst (mol%)	solvent	T (°C)	conv. (%)[c]	dr[d]	ee_{esterA} (%)[e]	ee_{esterB} (%)[e]	ee_{desym} (%)[e,f]	ee_{thiol} (%)[e]	S[g]
1	**2a** (0.5)	**10** (5)	MTBE	rt	49	-	6.5	-	-	7	1.2
2	**2a** (0.5)	**11** (5)	MTBE	rt	50	-	9	-	-	9	1.3
3	**2a** (0.5)	**12** (5)	MTBE	rt	50	-	6	-	-	6	1.2
4	**2a** (0.5)	**13** (5)	MTBE	rt	50	-	13	-	-	13	1.5
5	**2a** (0.5)	**13** (5)	Et_2O	rt	50	-	14	-	-	14	1.5
6	**2a** (0.5)	**13** (5)	THF	rt	39	-	27	-	-	17	2.1
7	**2a** (0.5)	**13** (5)	CH_2Cl_2	rt	16	-	n.d.	-	-	-	-
8	**3a** (0.5)	**13** (5)	MTBE	rt	50	66.5:33.5	95	91	92	33	2.7
9	**3a** (0.5)	**13** (1)	MTBE	rt	49	67:33	97	88	94	33	2.7
10	**4** (0.5)	**13** (5)	MTBE	rt	50	n.d.	n.d.	n.d.	n.d.	21	1.8
11	**5** (0.5)	**13** (5)	MTBE	rt	50	60:40	n.d.	n.d.	n.d.	26	2.3
12	**3a** (0.5)	**14** (5)	MTBE	rt	49	70:30	97	87	94	41	3.9
13	**3a** (0.5)	**15** (5)	MTBE	rt	47	73:27	97	93	96	41	4.0
14	**3a** (0.5)	**16** (5)	MTBE	rt	44	79:21	97	90	96	45	5.6
15	**3a** (0.5)	**17** (5)	MTBE	rt	48	75:25	95	84	92	44	4.3
16	**3a** (0.5)	**18** (5)	MTBE	rt	48	89:11	95	68	90	60	8.5
17[a]	**3a** (0.5)	**18** (5)	MTBE	0	43	89:11	98	78	96	58	13.6
18[a]	**3a** (0.75)	**18** (10)	MTBE	0	62	79:21	95	90	94	93	11.6
19[b]	**3a** (0.75)	**18** (10)	MTBE	-30	54	89:11	98	84	96	90	25.5
20[b]	**2b** (0.75)	**18** (10)	MTBE	-30	33	-	n.d.	-	-	42 (85)[h]	17.9
21[b]	**3b** (0.75)	**18** (10)	MTBE	-30	4	-	n.d.	-	-	n.d.	n.d.
22[b]	**2a** (0.75)	**18** (10)	MTBE	-30	50	-	n.d.	-	-	68 (68)[h]	10.7

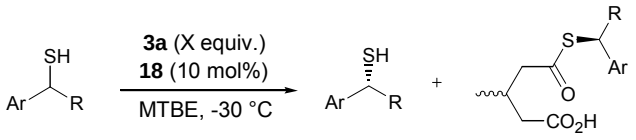
[a]48 h. [b]72 h. [c]Conversion was determined using CSP-HPLC, where conversion = 100 × $ee_{thiol}/(ee_{thiol} + ee_{thioester})$; the value of $ee_{thioester}$ was calculated using all four thioester stereoisomers. [d]Diastereomeric ratio = (**6-9a** + ***ent*-6-9a**):(**6-9b** + ***ent*-6-9b**). [e]Determined by CSP-HPLC, see supporting information. [f]Desymmetrisation efficiency: the enantiomeric excess of the desymmetrised product if the combined thioester products were substituted by an achiral (non-hydroxide) nucleophile, calculated as 100 x [(**6-9a** + **6-9b**) – (***ent*-6-9a** + ***ent*-6-9b**)] / [(**6-9a** + **6-9b**) + (***ent*-6-9a** + ***ent*-6-9b**)]. [g]S = enantioselectivity ($k_{fast/kslow}$, see ref. 1). [h]Value in parenthesis refers to the *ee* of the thiol obtained after deprotection *via* cleavage of the combined thioester products.

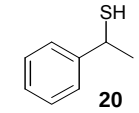
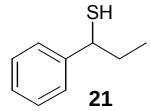
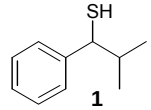
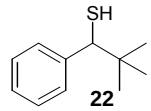
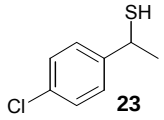
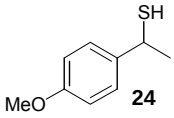
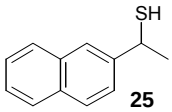
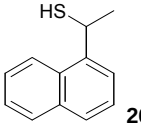
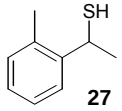
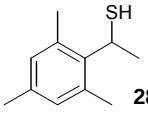
While these results represented the first examples of direct catalytic asymmetric KR of a thiol, the selectivity achieved was not at a synthetically useful level. Faced with this failure, we attempted the KR reactions using 3-

substituted achiral anhydride electrophiles **3a-5**. While this complicated matters considerably, as now control over the formation of 4 possible thioester diastereomers is required, we knew that organocatalytic, stereoselective additions of achiral nucleophiles to 3-substituted glutaric anhydrides were possible[25-34] and therefore posited that the additional control associated with the catalyst guiding the nucleophile to a single *prochiral* carbonyl group of the anhydride could result in improved potential for enantiodiscrimination of the thiol nucleophile. In addition, it allowed for the possibility of a conceptually novel type of catalytic process where both kinetic resolution and anhydride desymmetrisation *occur simultaneously*. Gratifyingly, this proved to be the case – use of anhydrides **3a-5** resulted in more enantioselective acylations (entries 8-11), with methyl glutaric anhydride (**3a**) proving optimal. Using this electrophile the resolved thiol could be isolated in 33% *ee* at 50% conversion (using either 1 or 5 mol% of catalyst **13**), corresponding to S = 2.7. Furthermore, product esters **7a** and **7b** were both formed with excellent enantioselectivity (>90% *ee*) and with encouraging diastereocontrol (67:33 dr, entry 8). With respect to the anhydride, the desymmetrisation aspect of the reaction was highly selective – the parameter ee_{desymm} (Table 1) represents the percentage excess of products derived from attack of the thiol **1** at one prochiral anhydride carbonyl moiety over the other (*i.e.* the enantiomeric excess of the desymmetrised product if the combined thioester diastereomers were substituted by an achiral (non-hydroxide) nucleophile without racemisation). It is also noteworthy that in the presence of triethylamine as an achiral catalyst the diastereoselectivity is reversed, with **19** as the major diastereomer.

Next the steric and electronic characteristics of the catalyst were systematically varied through the synthesis and evaluation of sulfonamides **14-17**. While the electron deficient pentafluorophenyl-substituted catalyst fared a little better than **13**, less acidic analogues **15-17** respectively possessed enhanced selectivity profiles (entries 12-15). Given the superiority of the hindered promoter **16**, it was decided to accentuate the steric bulk of the sulfonamide further *via* the synthesis of the novel catalyst **18**, which proved almost as active as **13** yet promoted the acylation with a synthetically useful KR selectivity of 8.5 (entry 16). Further optimisation of the reaction conditions (entries 17-19) resulted in the KR of thiol **1** with outstanding selectivity (S = 25.5) – allowing the isolation of resolved **(*R*)-1** in 90% *ee* at 54% conversion, along with ester **7a** (formed as the major diastereomer, 89:11 dr) in 98% *ee*, with an excellent attendant ee_{desymm} of 96% (entry 19). Thus, under optimum conditions **18** is capable of mediating *the highly efficient and selective KR of a substrate class previously outside the orbit of direct enantioselective catalytic acylation, with the simultaneous desymmetrisation of a synthetically useful class of inexpensive achiral anhydride acylating agent – also with excellent enantioselectivity*. To demonstrate that the desymmetrisation and kinetic resolution processes are synergistic, we next carried out the process under optimum conditions using the non-prochiral anhydrides **2a**, **2b** and **3b** (entries 20-22). Kinetic resolution was either too slow or proceeded with lower enantioselectivity using these electrophiles.

Table 2: Evaluation of substrate scope



entry	substrate	X	time (h)	conv. (%)[a]	ee_{thiol} (%)[b]	S[c]	abs. config.[d]
1	 **20**	0.75	68	63	97	14.5	(*R*)
2	 **21**	0.75	74	56	91	19.0	(*R*)
3[e]	 **1**	0.75	68	54	90	25.5	(*R*)
4[f]	 **22**	0.75	96	52	94	51.5	(*R*)
5	 **23**	0.75	72	65	95	10.7	(*R*)
6	 **24**	0.90	120	56	87	15.0	(*R*)
7	 **25**	0.75	74	58	82	9.7	(*R*)
8[g]		0.75	72	45	59	11.8	(*R*)
9[h]	 **26**	0.75	96	51	90	36.6	(*R*)
10	 **27**	0.75	48	50	95 (94)[j]	126.0	(*R*)
11[i]		0.75	48	50	98 (96)[j]	265.0	(*R*)
12[k]	**28**	0.75	48	43	75 (98)[j]	275.0	(*R*)

[a]Refers to conversion, determined using CSP-HPLC, where conversion = 100 × ee_{thiol}/(ee_{thiol} + $ee_{thioester}$). [b]Determined by CSP-HPLC, see supporting information. [c]S = enantioselectivity ($k_{fast/kslow}$, see ref. 1). [d]Refers to the absolute configuration of the recovered thiol product (see supporting information). [e]Data from Table 1. [f]A repeat of this experiment (conv. 52%, S = 50.4) resulted in the isolation of the unreacted (*R*)-thiol in 47% yield and 95% *ee* after chromatography. After aminolysis of the combined thioester products the (*S*)-thiol was obtained in 43% isolated yield and 86% *ee*. [g]Reaction at -40 °C. [h]A repeat of this experiment in which the combined thioester diastereomers were aminolysed resulted in the isolation of the corresponding hemiamide in 93% *ee*. [i]A repeat of this experiment (conv. 51%, S = 249.0) resulted in the isolation of the unreacted (*R*)-thiol in 48% yield and 99.6 % *ee* after chromatography. After aminolysis of the combined thioester products the (*S*)-thiol was obtained in 44% isolated yield and 95% *ee*. [j]Value in parenthesis refers to the *ee* of the thiol obtained after deprotection *via* cleavage of the combined thioester products. [k]Reaction at -45 °C.

Attention now turned to the question of substrate scope (Table 2). It was found that variation of the steric bulk of both the aromatic and aliphatic substituent is well tolerated by the catalyst – for example, α-Me, -Et, -^{i}Pr and -^{t}Bu

derivatives of benzyl mercaptan (*i.e.* **1** and **20**-**22**, entries 1-4) could be resolved with excellent selectivity (up to S > 50), resulting in the isolation of the unreacted thiol with >90% *ee* at *ca*. 50% conversion. A strong correlation between increasing aliphatic substituent bulk and selectivity was observed; however it is noteworthy that even the challenging substrate **20** (where the steric discrepancy between the two carbon-based substituents is smallest) could be resolved with synthetically useful selectivity. Variation of the characteristics of the aromatic substituent produced interesting results – substitution in the *para*-position either slightly reduces or has no impact on enantioselectivity (**23**-**25**, entries 5-7), while steric bulk at the *ortho*-position dramatically improved the KR; in optimum cases this resulted in levels of enantiodiscrimination (S >> 100) more usually associated with the enzymatic KR of alcohols (**26**-**28**, entries 8-12).

To demonstrate the potential utility of this methodology, we carried out the KR of thiol **28** (0.80 mmol) with catalyst **18** in the presence of achiral anhydride **4**, which furnished **(*R*)-28** (0.39 mmol, 99% *ee*) and the ring-opened product **29** (0.40 mmol) with excellent efficiency at 51% conversion (Figure 1). Thioester **29** (as a mixture of diastereomers) was then treated with aqueous ammonia, resulting in its cleavage to afford the other thiol enantiomer **(*S*)-28** (96% *ee,* 0.35 mmol) and the aminolysed product **(*S*)-30** (97% *ee*, 0.38 mmol), again with high efficiency. Hemiamide **(*S*)-30** is a precursor which can be converted in a single step to the (*R*)-antipode of the anticonvulsive agent Pregabalin[34] (Figure 1) and thus this sequence - in addition to serving as a highly efficient KR of **28** - constitutes a rapid and convenient formal synthesis of the 'blockbuster' drug[35] (marketed as 'Lyrica') antipode. In a similar fashion we also resolved thiol **31**, which constitutes the structural (stereocentre containing) core of the leukotriene receptor antagonist (*R*)-Montelukast – a drug used in the treatment of asthma and seasonal allergies (marketed as 'Singulair'). Racemic thiol **31** proved to be a challenging substrate which could nonetheless be smoothly resolved in the presence of catalyst **18** and anhydride **3a** to afford the pharmaceutically relevant (*R*)-thiol antipode in excellent enantiomeric excess (Figure 2).

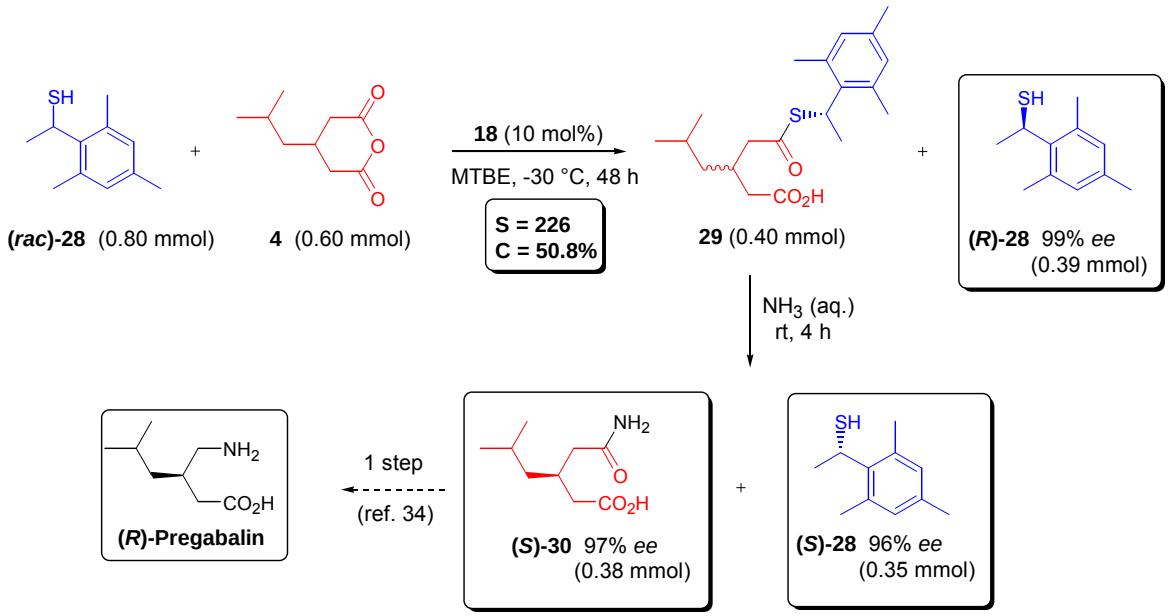


Figure 1: KR of thiol 28 with simultaneous enantioselective synthesis of a (*R*)-Pregabalin precursor

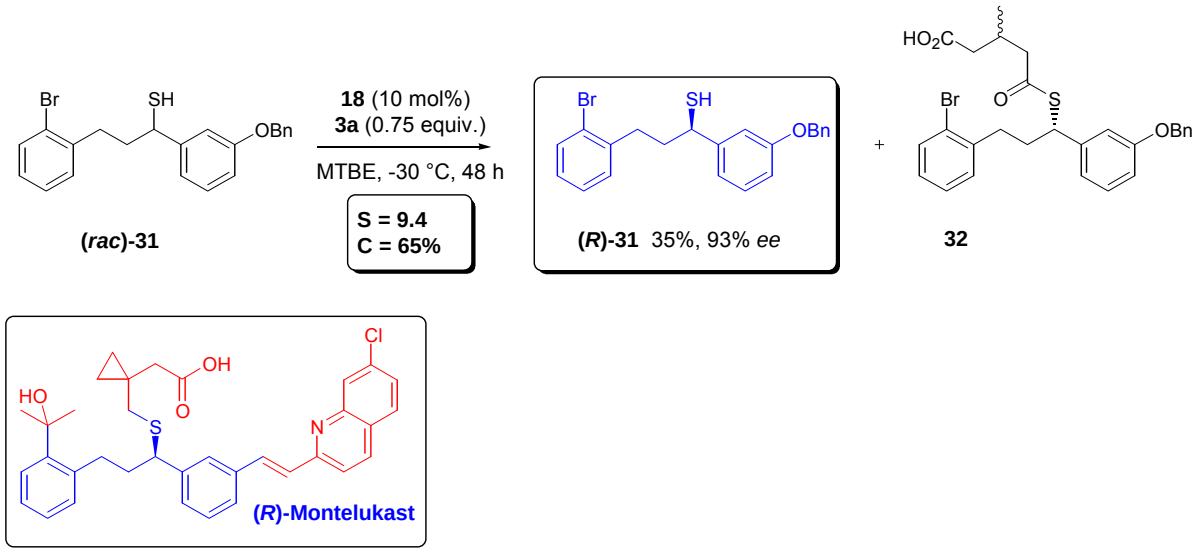


Figure 2: Synthesis of the (*R*)-Montelukast structural core via a catalytic thiol-KR

By analogy with both earlier work from Oda,[36] and more recent computational studies concerning the alcoholysis of anhydrides by catalyst **13** by Song *et al.*[33] we propose that catalyst **18** operates *via* a bifunctional mechanism in which stabilisation of developing positive charge on the thiol sulfur atom and developing negative charge on the anhydride carbonyl moiety undergoing nucleophilic attack is mediated by the basic quinuclidine ring and the hydrogen bond donating sulfonamide moiety respectively. It is interesting to note that the less acidic *sec*-phenylethanol (the alcohol

analogue of **20**) did not open anhydride **3a** in the presence of **18**, which would strongly support a considerable degree of proton transfer to the quinuclidine ring in the rate-determining transition state of these reactions.

Conclusions

In conclusion we have developed the novel sulfonamide catalyst **18**, which promotes the highly enantioselective (S > 10) direct acylative KR of a *sec*-thiols for the first time, allowing their isolation in >90% *ee* at *ca*. 50% conversion. Under optimum conditions at low catalyst loadings the selectivity (k_{fast}/k_{slow}) of these processes is in the range of 50 - 275, thus using the artificial catalyst **18** it is possible to achieve levels of enantiodiscrimination more usually associated with acylative KR by biological catalysts, using a substrate class not hitherto demonstrated to be generally amenable to enzyme-mediated direct acylative KR. In addition, the thiol-KR is accompanied by a synergistic, simultaneous desymmetrisation of an achiral anhydride electrophile – which occurs with excellent levels of enantioselectivity on a par with those associated with the best anhydride desymmetrisation methodologies in the literature.[37,38,39,40] This catalytic desymmetrisation of an electrophile while it kinetically resolves a nucleophile is, to the best of our knowledge, a hitherto unreported phenomenon which possesses excellent potential as a tool to considerably improve upon both the synthetic utility and atom economy of acylative KR processes. Studies aimed at further exploration of the scope of this strategy are underway in our laboratories.

Methods

Tandem KR-desymmetrisation procedure: A 20 mL reaction vial containing a stirring bar was charged with 3-methylglutaric anhydride (**3a**) (28.8 mg, 0.225 mmol) and **18** (17.7 mg, 0.030 mmol). The reaction vial was flushed with argon and fitted with a septum. MTBE was then added *via* syringe (1.5 mL, 0.2 M) and the solution cooled to -30 °C. The relevant thiol (0.30 mmol) was added *via* syringe and the resulting solution stirred for the time indicated in Table 2. The reaction mixture was then subjected to column chromatography and the separated unreacted thiol and thioester products were then derivatised (as their acrylonitrile Michael adduct and *o*-nitrophenyl ester respectively) to render them suitable for CSP-HPLC analysis (see supplementary information for details).

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Author contributions

S.J.C., B.P. and A.P. designed the research, S. J. C. analysed the data and prepared the manuscript, B.P., A.P. and C. J. O' C. performed the experimental work. All authors discussed the results and commented on the manuscript.

Additional information

Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://npg.nature.com/reprintsandpermissions/. Correspondence and requests for materials should be addressed to S.J.C.

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