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Synergistic organocatalysis in the kinetic resolution of secondary thiols with concomitant desymmetrization of an anhydride

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Kinetic resolution is an important method for the separation of racemates into their component enantiomers. Thiols are precursors to a variety of organosulfur compounds, with high utility in both chemistry and chemical biology, yet there is a surprising dearth of methodologies for their direct and efficient catalytic kinetic resolution. Here, we demonstrate an organocatalytic process involving the highly enantioselective desymmetrization of an achiral electrophile with the simultaneous kinetic resolution of a racemic thiol. The preparative potential of the methodology is exemplified by the synthesis of a drug precursor antipode in excellent yield and enantioselectivity as a by-product of a process that also resolves a *sec*-thiol substrate with a selectivity of $S = 226$ (that is, both thiol antipodes produced in >95% *ee* at 51% conversion). In a second example a racemic *sec*-thiol representing the stereocentre-containing core of the anti-asthma drug (*R*)-Montelukast was resolved with synthetically useful selectivity under mild conditions.

One of the most convenient methods for the rapid isolation of enantiopure secondary alcohols is the kinetic resolution (KR) of the corresponding racemic materials through enantioselective acylation[1,2]. Initially this was carried out using biological catalysts[3,4]. However, in recent years, several efficient and selective artificial organocatalysts have become available for these processes[5–14]. Although 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[17–19]. Baker's yeast has been used to resolve a chiral thiol in the presence of glucose, but 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. In these, Cesti and colleagues[21] and Hult and colleagues[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 use one of the lipases to promote the direct acylative KR of thiols failed to produce enantio-enriched products[22].

Although enantio-enriched thiols can be synthesized from the corresponding alcohols, this simply makes one reliant on (and limited by) the availability of the desired alcohol substrate in an enantiopure form. In addition, care must be taken[23] where a substrate (or its derivatives) is capable of racemization. For example, before this study could begin a sample of thiol **1** (Table 1) in an enantiopure form was required so that both enantiomers of (***rac*)-1** could be unambiguously identified by chiral stationary phase-(CSP) HPLC analysis. Commercially available (*R*)-1-phenyl-2-methyl-propanol (>99% *ee*) was therefore taken and subjected 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. Although it was clear at the outset that there were particular difficulties associated with the development of an organocatalytic enantioselective acylation protocol for thiol substrates relative to alcohols (for example, 'softer' nucleophile, greater distance between the reacting heteroatom and the stereocentre, and lower heteroatom pK_a), the paucity of methodologies available in the literature for the catalytic asymmetric synthesis of enantio-enriched thiols—and for the KR of thiols in particular—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 desymmetrization of *meso* glutaric anhydrides[25–28] with achiral alcohol[29] and thiol[30] nucleophiles (a process first reported using artificial catalysts by Nagao and colleagues[31]) at ambient temperature using low catalyst loadings[32,33]. For the 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 have a significant role in determining the efficacy of the desymmetrization process from a stereoselectivity standpoint, then these putative interactions could potentially also be used 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 **5**–**7** and sulfonamide **8**, which we[29,30] and Song and colleagues[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 a low catalyst loading (5 mol%), but resulted in products of low enantiomeric excess (entries 1–4). Of the four catalysts tested, sulfonamide **8** proved to be superior to the (thio)urea

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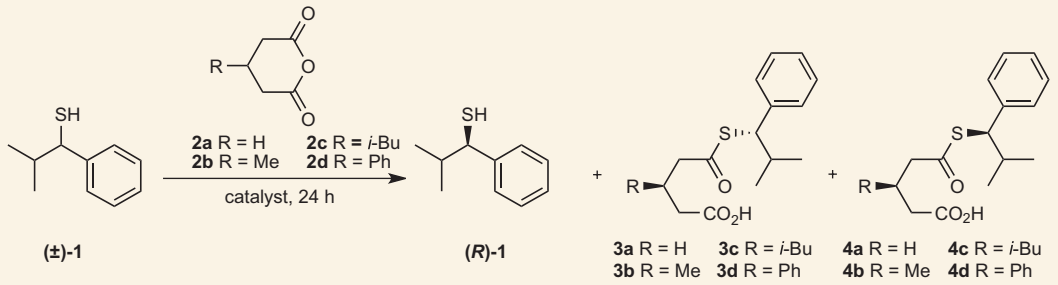
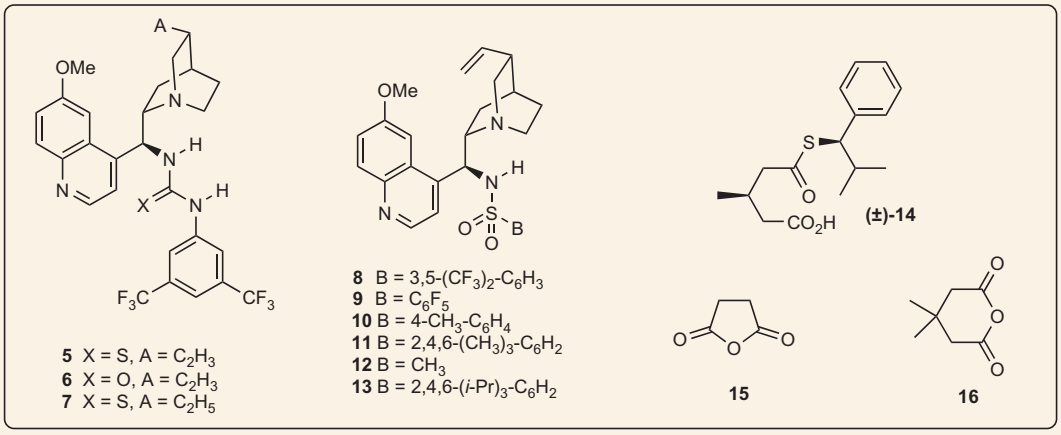
Table 1 | Kinetic resolution of thiol 1 with simultaneous desymmetrization of achiral anhydrides.





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

*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. †Diastereomeric ratio = (**3a–d** + ***ent*-3a–d**):(**4a–d** + ***ent*-4a–d**). ‡Determined by CSP-HPLC, see Supplementary Information. §Desymmetrization efficiency: the enantiomeric excess of the desymmetrized product if the combined thioester products were substituted by an achiral (non-hydroxide) nucleophile, calculated as 100 × [(**3a–d** + **4a–d**)-(***ent*-3a–d** + ***ent*-4a–d**)]/[(**3a–d** + **4a–d**) + (***ent*-3a–d** + ***ent*-4a–d**)]. ‖*S* = enantioselectivity ($k_{fast/kslow}$, see ref. 1). ¶48 h. #72 h. **Values in parentheses refer to the *ee* of the thiol obtained after deprotection through cleavage of the combined thioester products. rt = room temperature; n.d. = not determined.

derivatives and could promote KR with a very modest selectivity (k_{fast}/k_{slow})[1] of 1.5 (13% *ee* at 50% conv., entry 4). Further experimentation identified methyl *tert*-butylether (MTBE) as the optimal solvent overall, although the KR of **1** was slower but more selective in tetrahydrofuran (THF) (entries 4–7).

Although 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 **2b–d**. Although this complicated matters considerably, as control over the formation of four possible thioester diastereomers is then 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 enantio discrimination of the thiol nucleophile. In addition, it allowed for the possibility of a conceptually novel type of catalytic

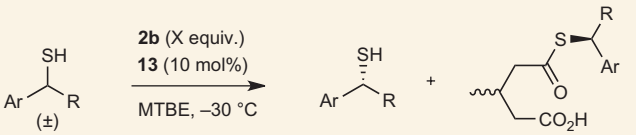
process in which both KR and anhydride desymmetrization occur simultaneously. Gratifyingly, this proved to be the case, with the use of anhydrides **2b**–**d** resulting in more enantioselective acylations (entries 8–11), with methyl glutaric anhydride (**2b**) proving optimal. Using this electrophile, the resolved thiol could be isolated in 33% *ee* at 50% conversion (using either 1 or 5 mol% of catalyst **8**), corresponding to $S = 2.7$. Furthermore, product esters **3b** and **4b** were both formed with excellent enantioselectivity (>90% *ee*) and with encouraging diastereocontrol (67:33 dr, entry 8). With respect to the anhydride, the desymmetrization aspect of the reaction was highly selective. The parameter ee_{desymm} (Table 1) represents the percentage excess of products derived from attack of thiol **1** at one prochiral anhydride carbonyl moiety over the other (that is, the enantiomeric excess of the desymmetrized product if the combined thioester diastereomers were substituted by an achiral (non-hydroxide) nucleophile without racemization). It is also noteworthy that in the presence of triethylamine as an achiral catalyst the diastereoselectivity is reversed, with (±)-**14** as the major diastereomer.

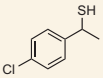
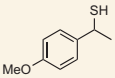
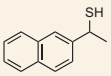
The steric and electronic characteristics of the catalyst were then systematically varied through the synthesis and evaluation of sulfonamides **9**–**12**. Although the electron-deficient pentafluorophenyl-substituted catalyst fared a little better than **8**, less acidic analogues **10**–**12** had enhanced selectivity profiles (entries 12–15). Given the superiority of the hindered promoter **11**, it was decided to accentuate the steric bulk of the sulfonamide further through the synthesis of the novel catalyst **13**, which proved almost as active as **8**, yet promoted the acylation with a synthetically useful KR selectivity of 8.5 (entry 16). Further optimization 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 **3a** (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, **13** 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 desymmetrization of a synthetically useful class of inexpensive achiral anhydride acylating agent, also with excellent enantioselectivity. To demonstrate that the desymmetrization and KR processes are synergistic, we next carried out the process under optimum conditions using the non-prochiral anhydrides **2a**, **15** and **16** (entries 20–22). KR either was too slow or proceeded with lower enantioselectivity using these electrophiles.

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 (that is, **1** and **17**–**19**, 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 ∼50% conversion. A strong correlation between increasing aliphatic substituent bulk and selectivity was observed; however, it is noteworthy that even the challenging substrate **17** (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 (**20**–**22**, entries 5–8), whereas steric bulk at the *ortho*-position dramatically improved the KR. In optimum cases this resulted in levels of enantio-discrimination ($S \gg 100$) more usually associated with the enzymatic KR of alcohols (**23**–**25**, entries 9–12).

To demonstrate the potential utility of this methodology, we carried out the KR of thiol **25** (0.80 mmol) with catalyst **13** in the presence of achiral anhydride **2c**, which furnished ***(R)*-25** (0.39 mmol, 99% *ee*) and the ring-opened product **26** (0.40 mmol) with excellent efficiency at 51% conversion (Fig. 1). Thioester **26** (as a mixture of diastereomers) was then treated with aqueous ammonia, resulting in its cleavage to afford the other thiol enantiomer ***(S)*-25** (96% *ee*, 0.35 mmol) and the aminolysed product ***(S)*-27** (97% *ee*, 0.38 mmol), again with high efficiency. Hemiamide ***(S)*-27** is a

Table 2 | Evaluation of substrate scope.



Entry	Substrate	X	Time (h)	Conv. (%)*	ee_{thiol} (%)†	S‡	Abs. config.§
1	 **17**	0.75	68	63	97	14.5	(*R*)
2	 **18**	0.75	74	56	91	19.0	(*R*)
3‖	 **1**	0.75	68	54	90	25.5	(*R*)
4¶	 **19**	0.75	96	52	94	51.5	(*R*)
5	 **20**	0.75	72	65	95	10.7	(*R*)
6	 **21**	0.90	120	56	87	15.0	(*R*)
7	 **22**	0.75	74	58	82	9.7	(*R*)
8#		0.75	72	45	59	11.8	(*R*)
9**	 **23**	0.75	96	51	90	36.6	(*R*)
10	 **24**	0.75	48	50	95 (94)‡‡	126.0	(*R*)
11††	 **25**	0.75	48	50	98 (96)‡‡	265.0	(*R*)
12§§		0.75	48	43	75 (98)‡‡	275.0	(*R*)

*Refers to conversion, determined using CSP-HPLC, where conversion = $100 \times ee_{thiol}/(ee_{thiol} + ee_{thioester})$. †Determined by CSP-HPLC, see supporting information. ‡S = enantioselectivity ($k_{fast/kslow}$, see ref. 1). §Refers to the absolute configuration of the recovered thiol product (see Supplementary Information). ‖Data from Table 1. ¶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*. #Reaction at −40 °C. **A repeat of this experiment in which the combined thioester diastereomers were aminolysed resulted in the isolation of the corresponding hemiamide in 93% *ee*. ††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*. ‡‡Values in parentheses refer to the *ee* of the thiol obtained after deprotection via cleavage of the combined thioester products. §§Reaction at −45 °C.

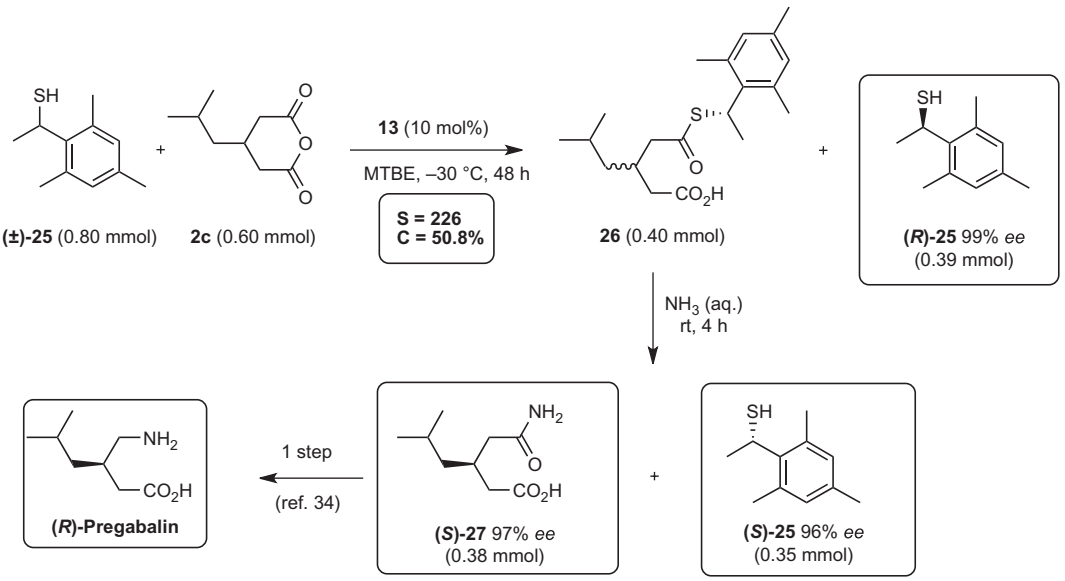


Figure 1 | Kinetic resolution of thiol 28 with simultaneous enantioselective synthesis of an (*R*)-Pregabalin precursor. Racemic thiol **25** can be reacted with anhydride **2c** in the presence of catalyst **13** to produce the unreacted (*R*)-enantiomer in excellent enantiomeric excess and isolated yield (based on a maximum of 50%), together with the mixture of thioesters **26**. When **26** are cleaved by aminolysis, both the (*S*)-thiol enantiomer and ***(S)*-27** can be isolated in excellent yield and >95% *ee*. Hemiamide ***(S)*-27** is a precursor (one step) from the (*R*)- enantiomer of the anticonvulsive drug Pregabalin. In this process (in contrast to the situation in most acylative KR processes where the acylating agent is discarded once cleaved from the fast-reacting substrate enantiomer), the acylating agent is thus converted to a value-added compound with excellent enantioselectivity although the thiol substrate is being resolved.

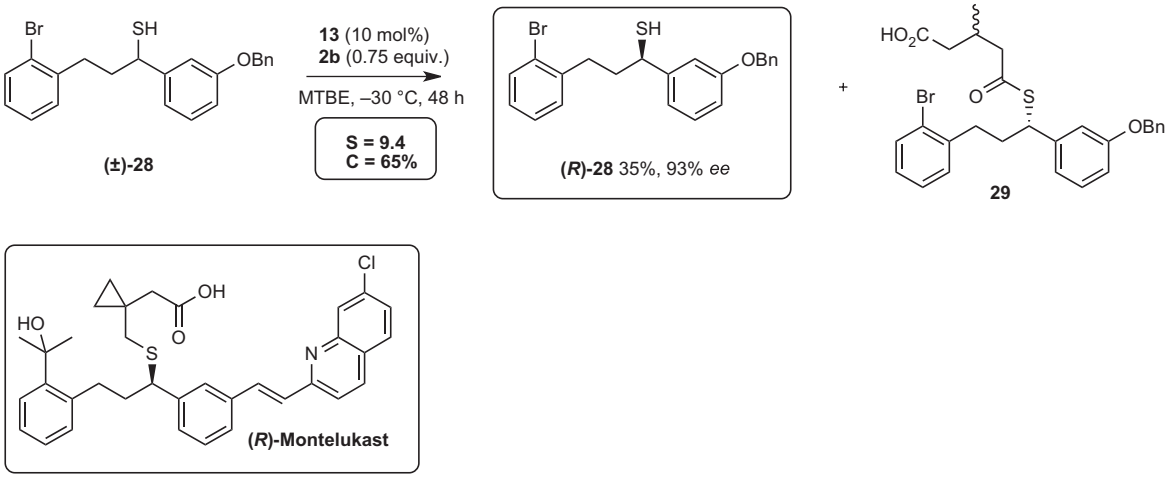


Figure 2 | Synthesis of the (*R*)-Montelukast structural core via a catalytic thiol kinetic resolution. Racemic thiol **28**, which can be readily synthesized from *o*-bromohydrocinammic acid, is resolvable with synthetically useful levels of enantioselectivity through acylation with anhydride **2b** in the presence of **13**. The resolved thiol ***(R)*-28** constitutes the stereocentre-containing core of the anti-asthma drug (*R*)-Montelukast.

precursor that can be converted in a single step to the (*R*)-antipode of the anticonvulsive agent Pregabalin[34] (Fig. 1) and thus this sequence—in addition to serving as a highly efficient KR of **25**—constitutes a rapid and convenient formal synthesis of the 'blockbuster' drug[35] (marketed as 'Lyrica') antipode.

In a similar fashion we also resolved thiol **28**, 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 **28** proved to be a challenging substrate that could nonetheless be smoothly resolved in the presence of catalyst **13** and anhydride **2b** to afford the pharmaceutically relevant (*R*)-thiol antipode in excellent enantiomeric excess (Fig. 2).

By analogy with both earlier work from Oda[36], and more recent computational studies concerning the alcoholysis of anhydrides with catalyst **8** by Song and colleagues[33] we propose that catalyst **13** operates through a bifunctional mechanism in which stabilization 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 **17**) did not open anhydride **2b** in the presence of **13**, which would strongly support a considerable degree of proton transfer to the quinuclidine ring in the rate-determining transition state of these reactions.

Conclusions

We have developed the novel sulfonamide catalyst **13**, which promotes the highly enantioselective ($S > 10$) direct acylative KR of

sec-thiols allowing their isolation in >90% *ee* at ~50% conversion. Under optimum conditions at low catalyst loadings, the selectivity (k_{fast}/k_{slow}) of these processes is in the range 50–275. Using the artificial catalyst **13** it is therefore 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 desymmetrization of an achiral anhydride electrophile, which occurs with excellent levels of enantioselectivity on a par with those associated with the best anhydride desymmetrization methodologies in the literature[37–40]. This catalytic desymmetrization of an electrophile while it kinetically resolves a nucleophile is, to the best of our knowledge, a hitherto unreported phenomenon that has excellent potential as a tool to considerably improve on both the synthetic utility and atom economy of acylative KR processes. Studies aimed at further exploration of the scope of this strategy are under way in our laboratories.

Methods

Tandem KR–desymmetrization procedure. A 20 ml reaction vial containing a stirring bar was charged with 3-methylglutaric anhydride (**2b**) (28.8 mg, 0.225 mmol) and **13** (17.7 mg, 0.030 mmol). The reaction vial was flushed with argon and fitted with a septum. MTBE was then added using a syringe (1.5 ml, 0.2 M) and the solution was cooled to −30 °C. The relevant thiol (0.30 mmol) was added with a syringe, and the resulting solution was 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 derivatized (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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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

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