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Catalytic Asymmetric Synthesis of Thiols

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Supporting Information

ABSTRACT: The synthesis of enantiopure thiols is of significant interest for industrial and academic applications. However, direct asymmetric approaches to free thiols have previously been unknown. Here we describe a novel organocascade that is catalyzed by a confined chiral phosphoric acid and furnishes *O*-protected *β*-hydroxythiols with excellent enantioselectivities. The method relies on an asymmetric thiocarboxylysis of *meso*-epoxides, followed by an intramolecular *trans*-esterification reaction. By varying the reaction conditions, the intermediate thioesters can also be obtained chemoselectively and enantioselectively.

Sulfur is a frequent constituent of pharmaceuticals, and its selective incorporation into complex molecular frameworks is highly relevant in medicinal chemistry.[1] Common approaches to the synthesis of sulfurous bioactive molecules rely on the nucleophilicity of thiol derivatives.[2] Remarkably, though, despite the value of enantiopure free thiols as building blocks, direct asymmetric approaches toward their preparation have been entirely elusive to date.[3] We now report an asymmetric organocascade that is catalyzed by a confined chiral phosphoric acid and delivers *O*-protected *β*-hydroxythiols in excellent enantioselectivities.

Developing enantioselective routes to *β*-hydroxythiols should be particularly rewarding, since they are often associated with privileged bioactivity, as illustrated with dihydrobenzoxathiins, cysteinyl leukotrienes, or the marketed drugs diltiazem and cevimeline (Figure 1).[4]

An asymmetric sulfhydrolysis of epoxides with hydrogen sulfide (H_2S) would arguably represent the most straightforward approach to *β*-hydroxythiols. However, due to the difficulties in exploiting H_2S, this transformation is still untapped, and most investigated routes rely on the thiolysis of epoxides. Much progress has recently been made in this area using metal-based Lewis acid catalysis and, very recently, also organocatalysis.[5,6] Despite such efforts, all these methodologies suffer the difficulty of satisfying both substrate generality and stereoselectivity. Moreover, thioether products are delivered in all cases, and their conversion into the desired free thiols generally requires additional steps and typically harsh conditions.[5c,6]

Very recently, we introduced a novel activation mode for carboxylic acids using Brønsted acid catalysis.[7] We reported the self-assembly between chiral phosphoric acid catalysts and carboxylic acids to exhibit a twofold beneficial effect: the enhancement of the nucleophilicity of the carboxylic acid molecule and a concurrent increase of the acidity of the heterodimer.[8] Presumably, the increased acidity observed is important for the activation of the electrophilic reaction partner in Brønsted acid organocatalysis. Broadening this activation mode to thiocarboxylic acids, a general and highly selective thiocarboxylysis of epoxides would be expected. Moreover, this reactivity should be extendable into an organocascade process,[9] in which the initially generated *β*-hydroxythioester undergoes an in situ Brønsted acid-catalyzed intramolecular *trans*-esterification reaction.[10] This sequence would give direct access to the free thiol moiety upon epoxide ring opening and represents an effective equivalent to the sulfhydrolysis reaction (Scheme 1).

At the outset of our investigation, we studied the proposed self-assembly between phosphoric acid **4a** (**TRIP**) and thiobenzoic acid (**2a**). NMR spectroscopic analysis indeed supported our speculations, confirming that in mixtures of the two acids in nonpolar media, an equilibrium toward heterodimer formation exists.[11] We therefore focused our attention

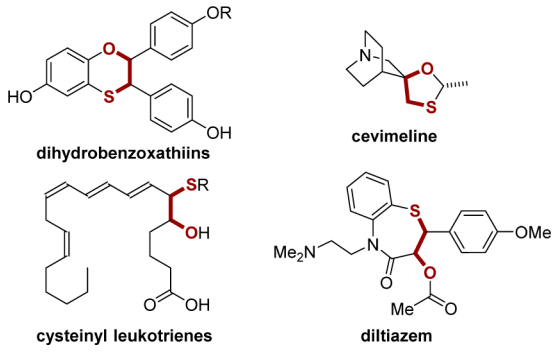
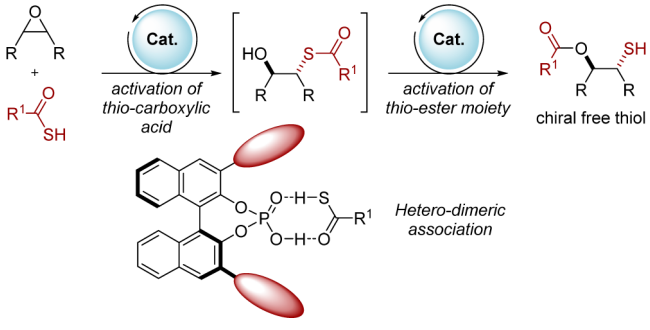


Figure 1. Bioactive molecules that incorporate a *β*-hydroxythiol framework.

Scheme 1. Organocascade Catalysis to *β*-Hydroxythiols



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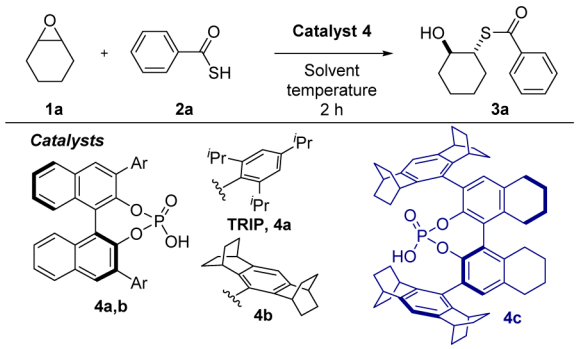
on developing the proposed methodology, choosing cyclohexene oxide **1a** as model substrate. Indeed, the reaction catalyzed by **TRIP** (**4a**) gave full conversion of the starting material into ring-opened product **3a** with promising enantioselectivity, yet the expected acyl-transfer product was not observed under these conditions (entry 1, Table 1). A screening of various reaction parameters was next performed to identify suitable conditions for the epoxide-opening reaction (Table 1).

Table 1. Establishing Suitable Reaction Conditions[a]



entry	catalyst	solvent	yield[b] (%)	er[c]
1	**TRIP**, **4a** (4 mol %)	CH_2Cl_2	>95	19.5:80.5
2	**4b** (4 mol %)	CH_2Cl_2	>95	14.5:85.5
3	**4c** (4 mol %)	CH_2Cl_2	>95	86:14
4	**4c** (4 mol %)	$CHCl_3$	>95	85:15
5	**4c** (4 mol %)	C_6H_6	>95	87.5:12.5
6	**4c** (4 mol %)	toluene	>95	90:10
7[d]	**4c** (4 mol %)	toluene	>95	95:5
8[e,g]	**4c** (4 mol %)	toluene	>95	98:2
9[e,g]	**4c** (2 mol %)	toluene	>95	98:2
10[e,g]	**4c** (1 mol %)	toluene	89	97.5:2.5
11[g]	**4c** (0.1 mol %)	toluene	>95	89.5:10.5
12[g]	**4c** (0.01 mol %)	toluene	48	85:15

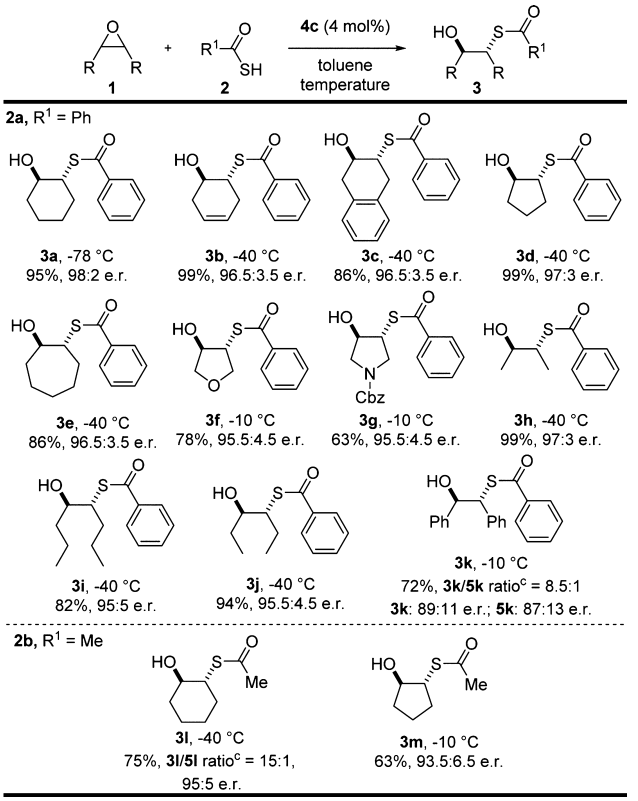
[a]Unless otherwise indicated, all reactions were carried out with substrate **1a** (0.05 mmol) and thiobenzoic acid **2** (0.08 mmol, 1.6 equiv) in 0.4 mL of solvent at room temperature. [b]Determined by ^{1}H NMR analysis. [c]Determined by HPLC on chiral stationary phase. [d]Reaction performed at −40 °C in 16 h. [e]Reaction performed at −78 °C. [g]Reaction time 2 days.

The enantioselectivity of the transformation was found to be affected by the steric hindrance of the catalyst pocket. In fact, confined chiral phosphoric acids bearing polycyclic substituents on the BINOL backbone, recently introduced by our group,[8b] were found to again outperform **TRIP** (entry 2, Table 1). Catalyst **4c**, with the hydrogenated BINOL-scaffold, promoted the reaction at room temperature, delivering the desired product in 86:14 enantiomeric ratio (er), and was selected for further optimization (entry 3, Table 1).[12] Extensive screening of the solvent and temperature revealed that full conversion and an excellent level of enantioselectivity can be achieved in toluene under cryogenic conditions (entry 8, Table 1). Remarkably, the reaction could be promoted by 1 mol % of catalyst **4c**, yielding the product in 89% yield and 97.5:2.5 er (entry 10, Table 1), while at room temperature, 100 ppm of catalyst loading was found to be the threshold for this activity (entry 12, Table 1).[13]

With the optimal conditions in hand, we next began investigating the substrate scope of this organocatalytic thiocarboxylysis of epoxides.

As shown in Chart 1, the transformation is rather general, and a large variety of *meso*-epoxides **1a**−**k** reacted with high

Chart 1. Thiocarboxylysis Reaction Scope[a,b]



[a]Isolated yields (%) and enantiomeric ratio (er); see Supporting Information for experimental details. [b]Enantiomeric ratio determined by HPLC on chiral stationary phase. [c]Product ratio determined by ^{1}H NMR analysis.

levels of stereocontrol. Six-membered-ring substrates **1a**−**c** delivered the corresponding *β*-hydroxythioesters **3a**−**c** in good to outstanding yields and excellent enantioselectivities. It is noteworthy that the reaction outcome is essentially unaffected by the ring size of the starting material, as proven by the high yields and optical purity of products **3d**,**e**. The presence of heteroatoms in the substrate scaffold is well tolerated (products **3f**,**g**), albeit with a small influence on the reactivity.[14] Acyclic substrates also reacted smoothly, providing *syn*-hydroxythioesters **3h**−**j** with excellent stereoselectivity. Notably, substrate **1h** gave product **3h** in outstanding yield (99%) and enantioselectivity (97:3 er), further confirming the potential of a confined catalysts in enantioselective transformations of very small substrates.[15] Furthermore, the challenging *cis*-stilbene oxide **1k** could be reacted under mild conditions, giving the product **3k** together with a minor amount of its thiol isomer **5k** in good yield and moderate optical purities (**3k**, 89:11 er; **5k**, 87:13 er).[16] Moreover, the asymmetric thiocarboxylysis could also be performed using thioacetic acid **2b**. Under similar reaction conditions, products **3l**,**m** were obtained with high levels of stereocontrol, albeit with slightly diminished reactivity.

The detection of significant amounts of thiol isomers **5k**,**l** (as shown in Chart 1) was important in our investigation since it

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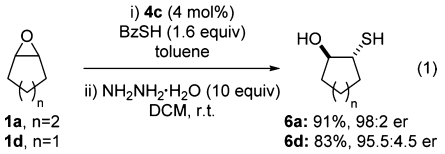
confirmed the feasibility of our originally designed organocascade. Apparently, the in situ sequence had been hampered with other substrates by a slow and rate-determing acyl-transfer step.

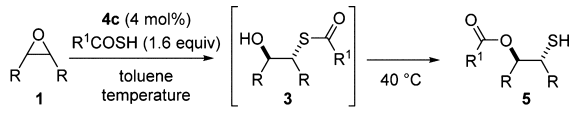
Consequently, we reinvestigated the reactions of all the previously tested substrates by simply elevating the reaction temperature upon consumption of the epoxide. Indeed, these conditions proved to be suitable for the catalytic activation of the thioester moiety, and the free thiol products were selectively obtained (Table 2).[17] Six- and seven-membered ring substrates smoothly underwent the cascade transformation (entries 1−5, Table 2), while the requirement for a *trans*-fused bicyclooctane intermediate prevented the formation of five-membered-ring products.[18] Linear products **5h−j** were also efficiently obtained in good yields and remarkable selectivity. In some cases, the optical purity of thiols **5** was found to be slightly lower than that of isolated alcohols **3**, shown above. This may be due to the conversion of a residual amount of epoxide starting material at higher temperature during the second step. A single recrystallization significantly improved the enantioenrichement of thiol **5k**, which was initially obtained in nearly quantitative yield but in only moderate enantioselectivity (entry 8, Table 2).

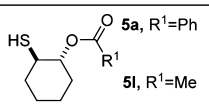
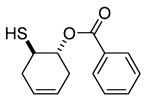
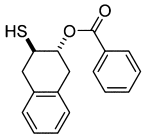
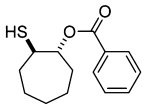
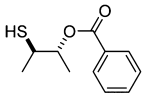
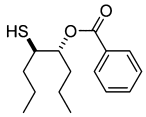
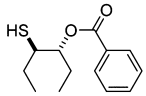
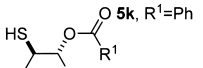
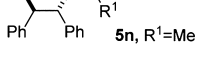
It is noteworthy that our transformation either can directly deliver organocascade products **5** or can be interrupted, giving intermediates **3**. This reaction control enables isolation of the same 1,2-hydroxythiol scaffold protected either on sulfur or on oxygen. Further, the initially formed products can also be deprotected in situ under mild conditions, yielding enantiopure 1,2-hydroxythiols. The overall methodology constitutes an equivalent of the long sought after asymmetric sulfhydrolysis reaction (eq 1).



In summary, we have developed a direct asymmetric approach to enantiopure free thiols. Expanding the concept of the organocatalytic activation of carboxylic acids, we disclose a catalytic organocascade that furnishes protected *β*-hydroxythiols. Employing a chiral confined phosphoric acid catalyst, this methodology shows wide substrate generality and high levels of stereoselectivity. Synthetic applicability is predicted, due to the possibility to control the position of the acyl protecting group. Further exploration in the field of carboxylic acids activation is currently in progress in our laboratories, especially regarding the use of thiocarboxylic acids as masked synthons of hydrogen sulfide in Brønsted acid catalysis.

Table 2. Organocascade Reaction Scope[a]



Entry	Product	Temp (°C)	Yield (%)	e.r.[b]
1	 **5a**, R^1=Ph	-78	86	98:2
2	**5l**, R^1=Me	-40	85	95:5
3	 **5b**	-40	98	96:4
4	 **5c**	-40	97	95:5
5	 **5e**	-40	80	96:4
6	 **5h**	-40	81	97:3
7	 **5i**	-40	82	94:6
8	 **5j**	-40	74	93.5:6.5
9	 **5k**, R^1=Ph	-10	99 (70)[c]	87:13 (98.5:1.5)[c]
10	 **5n**, R^1=Me	10[d]	63	86:14

[a]Unless otherwise indicated, all reactions were carried out with substrate **1** (0.1 mmol) and thiocarboxylic acid **2** (0.16 mmol, 1.6 equiv) in 0.8 mL of solvent. [b]Determined by HPLC or GC on chiral stationary phase. [c]Results in parentheses were obtained after a single recrystallization. [d]Temperature was maintained at 10 °C for all the reaction sequence.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional screening tables, detailed synthetic procedures, spectra, and HPLC traces for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832. (b) Moran, L. K.; Gutteridge, J. M.; Quinlan, G. J. *Curr. Med. Chem.* **2001**, *8*, 763. (c) Pachamuthu, K.; Schmidt, R. R. *Chem. Rev.* **2006**, *106*, 160.

(2) (a) *An Introduction to Organosulfur Chemistry*; Cremlin, R. J, Ed.; John Wiley & Sons Ltd.: Chichester, 1996. (b) *Sulfur Compounds: Advances in Research and Application*; Acton, A. Q., Ed.; ScholarlyEdition: Atlanta, GA, 2012. (c) Clayden, J.; MacLellan, P. *Beilstein J. Org. Chem.* **2011**, *7*, 582. (d) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 335. (e) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205.

(3) For alternative routes to enantioenriched thiols, see: (a) Peschiulli, A.; Procuranti, B.; O'Connor, C. J.; Connon, S. J. *Nat. Chem.* **2010**, *2*, 380. (b) Palomo, C.; Oiarbide, M.; Dias, F.; López, R.; Linden, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3307. (c) Palomo, C.; Oiarbide, M.; López, R.; González, P. B.; Gómez-Bengoa, E.; Saá, J. M.; Linden, A. *J. Am. Chem. Soc.* **2006**, *128*, 15236. (d) Overman, L. E.; Roberts, S. W.; Sneddon, H. F. *Org. Lett.* **2008**, *10*, 1485. (e) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev.* **2014**, *114*, 8807. (f) Meindertsma, A. F.; Pollard, M. M.; Feringa, B. L.; de Vries, J. G.; Minnaard, A. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2849. (g) Kimmel, K. L.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754. (h) Phelan, J. P.; Patel, E. J.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 11329. (i) Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 11846.

(4) (a) Blizzard, T. A.; DiNinno, F.; Chen, H. Y.; Kim, S.; Wu, J. Y.; Chan, W.; Birzin, E. T.; Yang, Y. T.; Pai, L.−Y.; Hayes, E. C.; DaSilva, C. A.; Roher, S. P.; Scheffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem.* **2005**, *15*, 3912. (b) *Prostaglandins, Leukotrienes and Lipoxins Biochemistry, Mechanism of Action and Clinical Applications*; Bailey, J. M., Ed.; Plenum Press: New York/London, 1985. (c) Nagao, T.; Sato, M.; Nakajima, H.; Kiyomoto, A. *Chem. Pharm. Bull.* **1973**, *21*, 92. (d) Ono, M.; Takamura, E.; Shinozaki, K.; Tsumura, T.; Hamano, T.; Yagi, Y.; Tsubota, K. *Am. J. Ophtalmol.* **2004**, *138*, 6.

(5) (a) Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 1643. (b) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783. (c) Wu, M. H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 5252. (d) Wu, J.; Hou, X.-L.; Dai, L.-X.; Xia, L.-J.; Tang, M.-H. *Tetrahedron: Asymmetry* **1998**, *9*, 3431. (e) Ogawa, C.; Wang, N.; Kobayashi, S. *Chem. Lett.* **2007**, *36*, 34. (f) Nandakumar, M. V.; Tschöp, A.; Krautscheid, H.; Schneider, C. *Chem. Commun.* **2007**, 2756. (g) Sun, J.; Yuan, F.; Yang, M.; Pan, Y.; Zhu, C. *Tetrahedron Lett.* **2009**, *50*, 548.

(6) Wang, Z.; Law, W. K.; Sun, J. *Org. Lett.* **2013**, *15*, 5964.

(7) For comprehensive reviews on asymmetric Brønsted acid catalysis, see: (a) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (b) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603. (c) Terada, M. *Synthesis* **2010**, 1929. (d) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999.

(8) (a) Monaco, M. R.; Poladura, B.; Diaz de los Bernardos, M.; Leutzsch, M.; Goddard, R.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 7063. (b) Monaco, M. R.; Prevost, S.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 8142.

(9) (a) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (b) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, S. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (c) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (d) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (e) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183.

(10) Qabaja, G.; Wilent, J. E.; Benavides, A. R.; Bullard, G. E.; Petersen, K. S. *Org. Lett.* **2013**, *15*, 1266.

(11) For the NMR association studies, see Supporting Information.

(12) Au-Yeung, T. T.-L.; Chan, S.-S; Chan, A. S. C. *Adv. Synth. Catal.* **2003**, *345*, 537.

(13) Presumably, the slight loss in enantioselectivity is derived from a slow background reactivity. Taking this phenomenon into account, the turnover number is 4320.

(14) Lower reactivity may be ascribable to the presence of competing hydrogen bond acceptors.

(15) Čorić, I.; List, B. *Nature* **2012**, *483*, 315.

(16) The different enantioenrichment between compounds **5k** and **3k** is due to the effect of the catalyst in the *trans*-esterification step.

(17) A control experiment on compound **3a** showed no conversion to **5a** in the absence of the catalyst. For detailed experimental results, see Supporting Information.

(18) For the unsuccessful reaction on five-membered-ring compounds, see Supporting Information.