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Weak Brønsted Acid–Thiourea Co-Catalysis: Enantioselective, Catalytic Protio-Pictet–Spengler Reactions

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Abstract

The development of one-pot imine formation and asymmetric Pictet–Spengler reactions co-catalyzed by a chiral thiourea and benzoic acid is described. Optically active tetrahydro-β-carbolines, ubiquitous structural motifs in biologically active natural products, are obtained in high ee directly from tryptamine and aldehyde precursors.

The Pictet–Spengler reaction is an important biosynthetic and laboratory method for the synthesis of tetrahydroisoquinolines and tetrahydro-β-carbolines, structural motifs in a diverse array of biologically active natural and unnatural products.^{1, 2} Whereas synthetically valuable diastereoselective Pictet–Spengler reactions are well known,³ catalytic, enantioselective variants have only recently been developed.⁴ Chiral Lewis acids have not proven to be generally useful for the Pictet–Spengler reaction, a likely result of catalyst inhibition by the Lewis basic product.⁵ Greater success has been achieved with Brønsted acid or hydrogen bond-donor catalysts, albeit with specialized substrates.⁶ Thus, asymmetric catalysis of Pictet–Spengler-type reactions has been reported with N-acyliminium ions^{4a} or N-sulphenyliminium ions,^{4b} or with substrates biased towards cyclization and against competing aldol pathways by gem-disubstitution adjacent to the reactive imine.^{4c} An enantioselective, catalytic Pictet–

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Supporting Information **Available:** Complete experimental procedures and characterization data for products and isolated intermediates. This material is available free of charge from <http://pubs.acs.org>.

Spengler protocol with broad substrate scope that affords unprotected tetrahydro- β -carboline products directly from simple tryptamine derivatives would represent a significant advance.

We have recently advanced a mechanistic model for asymmetric catalysis by thiourea derivatives in which substrate activation takes place via thiourea-mediated chloride abstraction to generate highly reactive N-acyliminium ions or oxocarbenium ions (Figure 1).⁷ This hypothesis suggests that a variety of other cationic intermediates, including protioiminium ions, could be activated towards enantioselective addition by analogous anion-binding mechanisms. In particular, we envisaged a catalytic cycle in which imine protonation is induced by a thiourea catalyst associated via H-bonding to the conjugate base of a weak Brønsted acid additive (Scheme 1).⁸ Cyclization of the highly reactive protioiminium ion followed by rearomatization would regenerate the Brønsted acid co-catalyst. Herein, we report that chiral thiourea derivatives in combination with benzoic acid promote catalytic asymmetric Pictet–Spengler reactions of electronically and sterically diverse imines, providing unprotected tetrahydro- β -carbolines in high ee and yield.

We selected 6-methoxytryptamine derivative **2a** as a model substrate. Methoxy-substituted tryptamine derivatives undergo cyclization in low enantioselectivity in the previously reported acyl-Pictet–Spengler reaction,⁹ a significant limitation given the prevalence of methoxy and hydroxy-substituted tetrahydro- β -carbolines in natural products.¹⁰ Moreover, elevated temperatures ($> -30\text{ }^{\circ}\text{C}$) were required for acyl-Pictet–Spengler reactions of aryl imines, conditions under which the thiourea catalyst was subject to decomposition via rapid *S*-acetylation. We reasoned that greater generality in the imine component would be possible in a non-acylative reaction. Imine **2a** was screened against a variety of representative thiourea catalysts¹¹ and achiral Brønsted acids. In combination with acetic acid (AcOH), catalysts **4a**¹² and **7a**¹³ provided tetrahydro- β -carboline **3a** in high yield and 85% and –87% ee, respectively (Scheme 2). Notably, no product was observed in the absence of AcOH.

These initial results were obtained at room temperature, conditions under which imine formation is rapid. We therefore explored an operationally simpler protocol involving one-pot imine formation and thiourea-catalyzed Pictet–Spengler reaction. Treatment of tryptamine **9a** and *p*-chlorobenzaldehyde with catalyst **4a** in toluene provided product **3a** in 88% ee and 54% yield (Table 1, entry 1). In contrast, sulfinamide **7a** was a poor catalyst under *in situ* imine formation conditions, providing product in only 13% yield. A systematic evaluation of the influence of catalyst structure on both enantioselectivity and rate revealed that valine-derived catalyst **4b** afforded optimal results (entry 2).¹⁴ This simple compound is prepared in 69% yield in three steps from commercially available *N*-methylbenzylamine and either (*D*)- or (*L*)-valine; only a single chromatographic purification is required. A screen of carboxylic acids revealed an increase in both enantioselectivity and rate with benzoic acid (PhCO₂H) (entry 2 vs. 4).¹⁵ Under the *in situ* imine-formation conditions, highest yields and enantioselectivities were obtained in reactions carried out at lower concentration (entries 4–6).

A variety of substituted benzaldehyde derivatives proved to be suitable substrates in combination with **9a**, providing tetrahydro- β -carboline products **3a–3g** in good-to-excellent ee's and yields (Table 2, entries 1–7). Substitution is tolerated at all ring positions of the aldehyde, with the shortest reaction times observed for *ortho*- and *meta*-substituted derivatives (entries 3–5). Less electron-rich tryptamines **9b** and **9c** also participated effectively in the condensation/cyclization reaction (89–99% ee), although elevated acid loadings and temperatures and extended reaction times were required to achieve useful product yields (entries 8–10).

Aliphatic aldehydes displayed unexpected reactivity with tryptamine **9a** in protio-Pictet–Spengler cyclizations catalyzed by **4b**. Isobutyraldehyde underwent rapid reaction under the

conditions optimized for aromatic aldehydes, affording product **3k** in 60% conversion and 88% ee after 4 hours at room temperature (entry 11). In contrast to aryl substrates, however, cyclization was also observed in the absence of PhCO₂H. In fact, the enantioselectivity increased to 94% in the absence of acid additive, although much longer reaction times were required (entry 12). Both linear and α -branched aldehydes participated effectively in cyclizations with **9a** (entries 12–14). In contrast, less nucleophilic tryptamines such as **9b** and **9c** were unreactive under neutral conditions. The basis for this intriguing difference in reactivity is not well understood at this stage. For substrates such as **9b**, use of acidic additive was necessary (e.g., entry 15), with reactions proceeding in high ee and in modest yield due to the competitive aldol pathways.

We have identified a readily accessible chiral thiourea catalyst that promotes highly enantioselective Pictet–Spengler reactions for electronically and structurally diverse substrates under mild and operationally simple conditions. This method provides unprotected tetrahydro- β -carbolines in one step from tryptamine and aldehyde derivatives. Our current efforts are directed toward elucidation of the mechanism of co-catalysis by achiral Brønsted acids, and application of this principle to other enantioselective reactions of synthetic interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. (a) Maresh J, Giddings L-A, Friedrich A, Loris EA, Panjikar S, Trout BL, Stockigt J, Peters B, O'Connor SE. *J. Am. Chem. Soc.* 2008;130:710–723. [PubMed: 18081287] (b) Luk LYP, Bunn S, Liscombe DK, Facchini PJ, Tanner ME. *Biochemistry* 2007;46:10153–10161. [PubMed: 17696451]
2. Cox ED, Cook JM. *Chem. Rev.* 1995;95:1797–1842.
3. (a) Zhou H, Liao X, Cook JM. *Org. Lett.* 2004;6:249–252. [PubMed: 14723540] For examples of diastereoselective Pictet–Spengler reactions of tryptophan derivatives and applications to total synthesis, see and references therein (b) Yamashita T, Kawai N, Tokuyama H, Fukuyama T. *J. Am. Chem. Soc.* 2005;127:15038–15039. [PubMed: 16248638] For an example of a diastereoselective Pictet–Spengler reaction of a tryptamine and a chiral aldehyde, see For a complete list of methods for the preparation of enantioenriched tetrahydro- β -carbolines, see the Supporting Information
4. (a) Taylor MS, Jacobsen EN. *J. Am. Chem. Soc.* 2004;126:10558–10559. [PubMed: 15327311] (b) Wanner MJ, van der Haas RNS, de Cuba KR, van Maarseveen JH, Hiemstra H. *Angew. Chem., Int. Ed.* 2007;46:7485–7487. (c) Seayad J, Seayad AM, List B. *J. Am. Chem. Soc.* 2006;128:1086–1087. [PubMed: 16433519] (d) Sewgobind NV, Wanner MJ, Ingemann S, de Gelder R, van Maarseveen JH, Hiemstra H. *J. Org. Chem.* 2008;73:6405–6408. [PubMed: 18616320]
5. Superstoichiometric amounts of diisopinocampheylchloroborane (Ipc₂BCl) promote Pictet–Spengler reactions of *N*- β -hydroxytryptamines. Yamada H, Kawate T, Matsumizu M, Nishida A, Yamaguchi K, Nakagawa M. *J. Org. Chem.* 1998;63:6348–6354. [PubMed: 11672269]
6. (a) Taylor MS, Jacobsen EN. *Angew. Chem., Int. Ed.* 2006;45:1520–1543. (b) Doyle AG, Jacobsen EN. *Chem. Rev.* 2007;107:5713–5743. [PubMed: 18072808]
7. (a) Raheem IT, Thiara PS, Peterson EA, Jacobsen EN. *J. Am. Chem. Soc.* 2007;129:13404–13405. [PubMed: 17941641] (b) Reisman SE, Doyle AG, Jacobsen EN. *J. Am. Chem. Soc.* 2008;130:7198–7199. [PubMed: 18479086]

8. For an example of a non-stereoselective application of this principle employing mandelic acid and achiral thiourea in the catalytic alcoholysis of styrene oxides, see: Weil T, Kotke M, Kleiner CM, Schreiner PR. *Org. Lett* 2008;10:1513–1516. [PubMed: 18366220]
9. 4 substrates: 44–86% ee. TaylorMS2005Harvard UniversityDissertation
10. Examples of methoxy and hydroxy substituted indole alkaloids include reserpine, tubulosine, and the eudimistin family of natural products. OsorioEJRobledoSMBastidaJCordellGAThe Alkaloids200866149159Academic PressSan Diego, CA1st ed.Chapter 2
11. The catalysts shown in Scheme 2 are available from Sigma-Aldrich.
12. Catalysts analogous to **4a** were first developed in the context of enantioselective Mannich-type reactions. Wenzel AG, Lalonde MP, Jacobsen EN. *Synlett* 2003;12:1919–1922.
13. Catalyst **7a** promotes enantioselective allylation of acylhydrazones. Tan KL, Jacobsen EN. *Angew. Chem., Int. Ed* 2007;46:1315–1317.
14. For a complete description of catalyst screening and reaction optimization, see the Supporting Information.
15. Stronger acids, such as hydrogen chloride and methanesulfonic acid, provided product in low yield and ee, potentially due to catalyst inhibition due to protonation of the Lewis basic product.

Figure 1.
Generation of *N*-acyliminium ion via anion-binding by a thiourea catalyst.

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Scheme 2.

Screen of representative (thio)urea catalysts.

Yield determined by ^1H NMR on a 0.05 mmol scale. Enantioselectivity determined by chiral SFC analysis of the *N*-Boc derivative.

Table 1
Optimization studies of the one-pot Pictet–Spengler reaction.

entry	catalyst	RCO ₂ H	[9a]	yield (%) ^a	ee (%) ^b
1	4a	AcOH	0.05 M	54	88
2	4b	AcOH	0.05 M	48	92
3	7a	AcOH	0.05 M	13	–79
4	4b	PhCO ₂ H	0.05 M	74	94
5	4b	PhCO ₂ H	0.10 M	60	93
6	4b	PhCO ₂ H	0.20 M	39	92

^aYield determined by ¹H NMR spectroscopy on a 0.05 mmol scale.

^bDetermined by chiral SFC analysis of the *N*-Boc derivative.

Table 2
Substrate scope of the thiourea and benzoic acid catalyzed Pictet–Spengler reaction.

<div> <div> <p>9a X = 6-MeO 9b X = 5-MeO 9c X = H</p> </div> </div>							
entry	tryptamine	R ^a	product	PhCO ₂ H (mol %)	t (h)	yield (%) ^b	ee (%) ^c
1	9a	<i>p</i> -ClC ₆ H ₄	3a	20	66	78	94
2	9a	<i>p</i> -FC ₆ H ₄	3b	20	78	81	92
3	9a	<i>p</i> -BrC ₆ H ₄	3c	20	74	79	94
4	9a	<i>m</i> -BrC ₆ H ₄	3d	20	19	87	94
5	9a	<i>o</i> -BrC ₆ H ₄	3e	20	11	74	95
6	9a	<i>p</i> -MeOC ₆ H ₄	3f	20	91	78	85
7	9a	Ph	3g	20	70	94	86
8 ^d	9b	<i>p</i> -ClC ₆ H ₄	3h	40	14 d	73	89
9 ^d	9b	<i>o</i> -BrC ₆ H ₄	3i	40	87	82	99
10 ^d	9c	<i>o</i> -BrC ₆ H ₄	3j	100	10 d	45	95
11	9a	<i>i</i> -Pr	3k	20	4	60 ^e	88
12	9a	<i>i</i> -Pr	3k	—	88	90	94
13	9a	CH(Et) ₂	3l	—	5 d	84	95
14	9a	<i>n</i> -pentyl	3m	—	18	74	86
15 ^d	9b	<i>i</i> -Pr	3n	20	36	39	88

^a All aldehydes were purified immediately prior to use. See the Supporting Information for details.

^b Isolated yield after column chromatography for 0.50 mmol-scale reactions, unless noted otherwise.

^c Determined by chiral SFC analysis of the *N*-Boc derivative.

^d Reaction carried out at 35 °C.

^e Yield determined by ¹H NMR spectroscopy on a 0.05 mmol scale.