

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

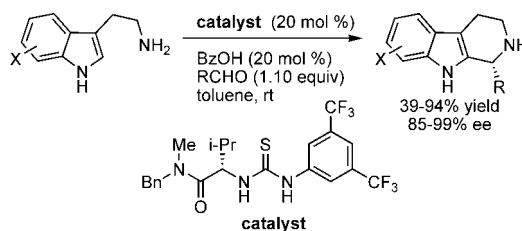
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## ABSTRACT



The development of one-pot imine formation and asymmetric Pictet–Spengler reactions cocatalyzed by a chiral thiourea and benzoic acid is described. Optically active tetrahydro- $\beta$ -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- $\beta$ -carbolines, structural motifs in a diverse array of biologically active natural and unnatural products.<sup>1,2</sup> Whereas synthetically valuable diastereoselective Pictet–Spengler reactions are well-known,<sup>3</sup> catalytic, enantioselective variants have only recently been developed.<sup>4</sup> 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.<sup>5</sup> Greater success has been achieved with Brønsted acid or hydrogen bond donor catalysts, albeit with specialized substrates.<sup>6</sup> Thus, asym-

metric catalysis of Pictet–Spengler-type reactions has been reported with *N*-acyliminium ions<sup>4a</sup> or *N*-sulfenyliminium ions<sup>4b</sup> or with substrates biased toward cyclization and against competing aldol pathways by *gem*-disubstitution adjacent to the reactive imine.<sup>4c</sup> An enantioselective, catalytic Pictet–Spengler protocol with broad substrate scope that affords unprotected tetrahydro- $\beta$ -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

(1) (a) Maresh, J. J.; Giddings, L.-A.; Friedrich, A.; Loris, E. A.; Panjikar, S.; Trout, B. L.; Stockigt, J.; Peters, B.; O'Connor, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 710–723. (b) Luk, L. Y. P.; Bunn, S.; Liscombe, D. K.; Facchini, P. J.; Tanner, M. E. *Biochemistry* **2007**, *46*, 10153–10161.

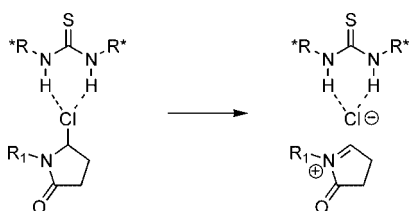
(2) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.

(3) For examples of diastereoselective Pictet–Spengler reactions of tryptophan derivatives and applications to total synthesis, see: (a) Zhou, H.; Liao, X.; Cook, J. M. *Org. Lett.* **2004**, *6*, 249–252, and references therein. For an example of a diastereoselective Pictet–Spengler reaction of a tryptamine and a chiral aldehyde, see: (b) Yamashita, T.; Kawai, N.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 15038–15039. (c) For a complete list of methods for the preparation of enantioenriched tetrahydro- $\beta$ -carbolines, see the Supporting Information.

(4) (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559. (b) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485–7487. (c) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086–1087. (d) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405–6408.

(5) Superstoichiometric amounts of diisopinocampheylchloroborane (Ipc<sub>2</sub>BCl) promote Pictet–Spengler reactions of *N*- $\beta$ -hydroxytryptamines. Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. *J. Org. Chem.* **1998**, *63*, 6348–6354.

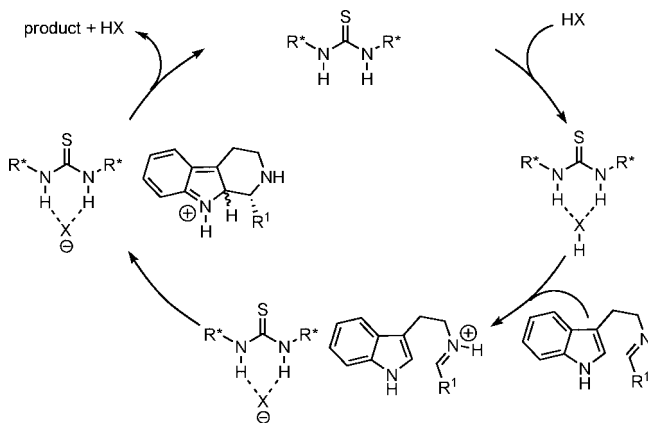
(6) (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743.



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

substrate activation takes place via thiourea-mediated chloride abstraction to generate highly reactive *N*-acyliminium ions or oxocarbenium ions (Figure 1).<sup>7</sup> This hypothesis suggests that a variety of other cationic intermediates, including protoiminium ions, could be activated toward 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).<sup>8</sup> Cyclization of the highly reactive protoiminium ion followed by rearomatization would regenerate the Brønsted acid cocatalyst. 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- $\beta$ -carbolines in high ee and yield.

#### Scheme 1. Brønsted Acid and H-Bond Donor Co-catalysis



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,<sup>9</sup> a significant limita-

tion given the prevalence of methoxy- and hydroxy-substituted tetrahydro- $\beta$ -carbolines in natural products.<sup>10</sup> 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 subjected to decomposition via rapid *S*-acetylation. We reasoned that greater generality in the imine component would be possible in a nonacylative reaction. Imine **2a** was screened against a variety of representative thiourea catalysts<sup>11</sup> and achiral Brønsted acids. In combination with acetic acid (AcOH), catalysts **4a**<sup>12</sup> and **7a**<sup>13</sup> provided tetrahydro- $\beta$ -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, sulfonamide **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).<sup>14</sup> 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 (PhCO<sub>2</sub>H) (entry 2 vs 4).<sup>15</sup> 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- $\beta$ -carboline products **3a–g** 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

(9) Four substrates: 44–86% ee. Taylor, M. S. Dissertation, Harvard University, 2005.

(10) Examples of methoxy- and hydroxy-substituted indole alkaloids include reserpine, tubulosine, and the eudimistin family of natural products. Osorio, E. J.; Robledo, S. M.; Bastida, J. *The Alkaloids*, 1st ed.; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 2008; Vol. 66, Chapter 2, pp 149–159.

(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, A. G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett* **2003**, 12, 1919–1922.

(13) Catalyst **7a** promotes enantioselective allylation of acyl hydrazones. Tan, K. L.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, 46, 1315–1317.

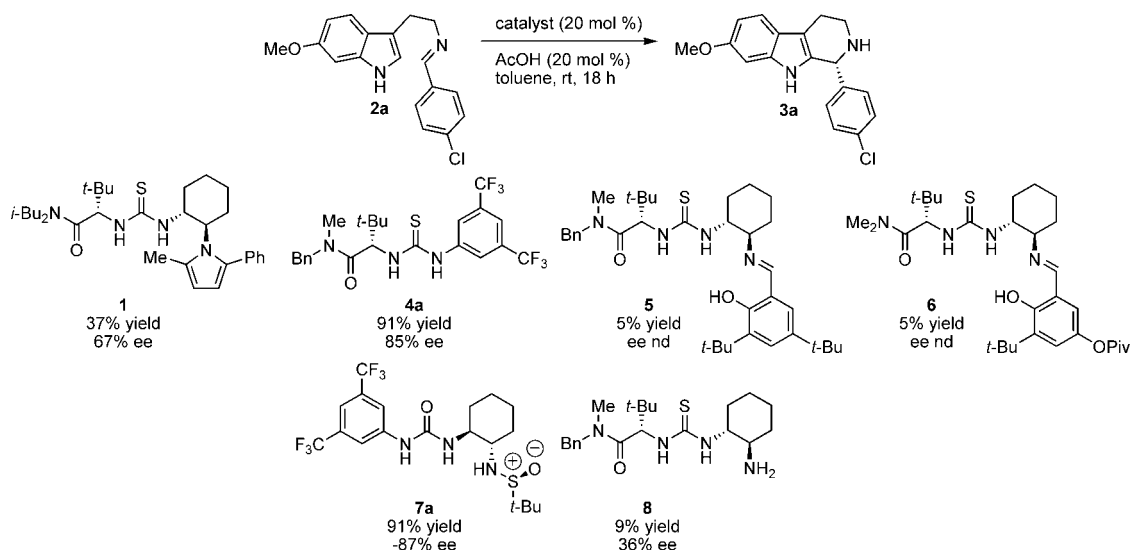
(14) For a complete description of catalyst screening and reaction optimization, see the Supporting Information.

(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.

(7) (a) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, 129, 13404–13405. (b) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, 130, 7198–7199.

(8) For an example of a nonstereoselective application of this principle employing mandelic acid and achiral thiourea in the catalytic alcoholysis of styrene oxides, see: Weil, T.; Kotke, M.; Kleiner, C. M.; Schreiner, P. R. *Org. Lett.* **2008**, 10, 1513–1516.

**Scheme 2. Screen of Representative (Thio)urea Catalysts<sup>a</sup>**



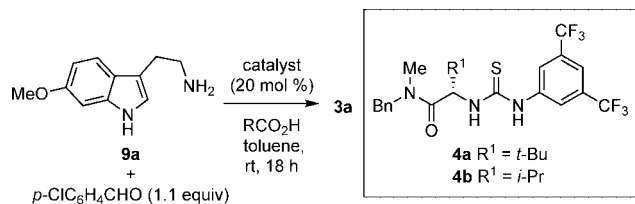
<sup>a</sup> Yield determined by <sup>1</sup>H NMR on a 0.05 mmol scale. Enantioselectivity determined by chiral SFC analysis of the *N*-Boc derivative.

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 h at room temperature (entry 11). In contrast to aryl substrates, however, cyclization was also observed in the absence of PhCO<sub>2</sub>H. 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

**Table 1.** Optimization Studies of the One-Pot Pictet–Spengler Reaction

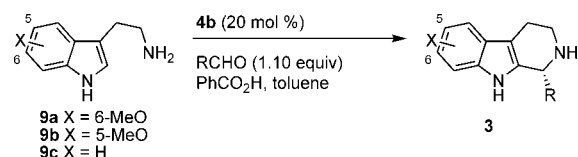


entry	catalyst	RCO <sub>2</sub> H	[ <b>9a</b> ] (M)	yield <sup>a</sup> (%)	ee <sup>b</sup> (%)
1	<b>4a</b>	AcOH	0.05	54	88
2	<b>4b</b>	AcOH	0.05	48	92
3	<b>7a</b>	AcOH	0.05	13	-79
4	<b>4b</b>	PhCO <sub>2</sub> H	0.05	74	94
5	<b>4b</b>	PhCO <sub>2</sub> H	0.10	60	93
6	<b>4b</b>	PhCO <sub>2</sub> H	0.20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

<sup>a</sup> Yield determined by <sup>1</sup>H NMR spectroscopy on a 0.05 mmol scale.

<sup>b</sup> Determined by chiral SFC analysis of the *N*-Boc derivative.

**Table 2.** Substrate Scope of the Thiourea and Benzoic Acid Catalyzed Pictet–Spengler Reaction



entry	tryptamine	R <sup>a</sup>	product	PhCO <sub>2</sub> H (mol %)	time (h)	yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	<b>9a</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>3a</b>	20	66	78	94
2	<b>9a</b>	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	<b>3b</b>	20	78	81	92
3	<b>9a</b>	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	<b>3c</b>	20	74	79	94
4	<b>9a</b>	<i>m</i> -BrC <sub>6</sub> H <sub>4</sub>	<b>3d</b>	20	19	87	94
5	<b>9a</b>	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	<b>3e</b>	20	11	74	95
6	<b>9a</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>3f</b>	20	91	78	85
7	<b>9a</b>	Ph	<b>3g</b>	20	70	94	86
8 <sup>d</sup>	<b>9b</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>3h</b>	40	14 d	73	89
9 <sup>d</sup>	<b>9b</b>	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	<b>3i</b>	40	87	82	99
10 <sup>d</sup>	<b>9c</b>	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	<b>3j</b>	100	10 d	45	95
11	<b>9a</b>	<i>i</i> -Pr	<b>3k</b>	20	4	60 <sup>e</sup>	88
12	<b>9a</b>	<i>i</i> -Pr	<b>3k</b>	0	88	90	94
13	<b>9a</b>	CH(Et) <sub>2</sub>	<b>3l</b>	0	5 d	84	95
14	<b>9a</b>	<i>n</i> -pentyl	<b>3m</b>	0	18	74	86
15 <sup>d</sup>	<b>9b</b>	<i>i</i> -Pr	<b>3n</b>	20	36	39	88

<sup>a</sup> All aldehydes were purified immediately prior to use. See the Supporting Information for details. <sup>b</sup> Isolated yield after column chromatography for 0.50 mmol scale reactions, unless noted otherwise. <sup>c</sup> Determined by chiral SFC analysis of the *N*-Boc derivative. <sup>d</sup> Reaction carried out at 35 °C. <sup>e</sup> Yield determined by <sup>1</sup>H NMR spectroscopy on a 0.05 mmol scale.

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- $\beta$ -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.

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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 via the Internet at <http://pubs.acs.org>.

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