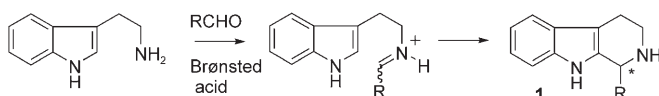


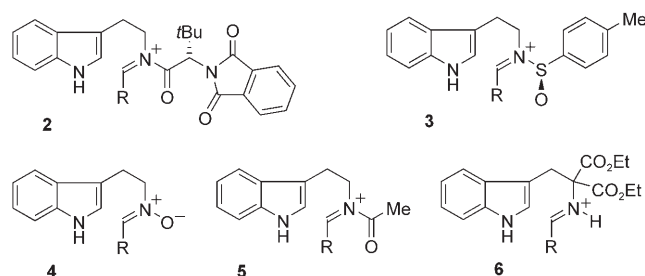
# Catalytic Asymmetric Pictet–Spengler Reactions via Sulfenyliminium Ions\*\*

Martin J. Wanner, Richard N. S. van der Haas, Kimberly R. de Cuba, Jan H. van Maarseveen, and Henk Hiemstra\*

The Pictet–Spengler condensation of tryptamine (or a substituted analogue) with an aldehyde, usually in the presence of an excess of a Brønsted acid,<sup>[1]</sup> is the reaction of choice for the preparation of tetrahydro- $\beta$ -carbolines (for example, **1**), a structural moiety present in many alkaloids and related biologically active molecules.<sup>[2]</sup>



Several strategies have been applied to the synthesis of tetrahydro- $\beta$ -carbolines in enantiomerically pure form. It is possible to start with an enantiomerically pure chiral tryptamine, such as a tryptophan derivative, or aldehyde; alternatively, the use of a chiral auxiliary attached to the nitrogen atom has been successful. Two remarkable examples are the cyclization of the *N*-acyliminium ion **2**, in which an  $\alpha$ -*N*-



phthaloylamino acid is used as a chiral auxiliary,<sup>[3]</sup> and the cyclization of the *N*-sulfinyliminium ion **3**, with the use of menthyl *p*-toluenesulfonate as a chiral reagent.<sup>[4]</sup> The former procedure proceeds with very high diastereoselectivity, but the chiral auxiliary can be removed only under relatively

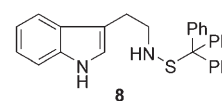
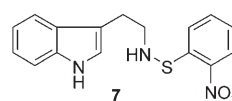
harsh reductive conditions. Lower selectivity is observed with the second method, but the diastereomers are readily separable, and the sulfinyl auxiliary can be cleaved easily by mild hydrolysis.

The first example of a reagent-controlled enantioselective Pictet–Spengler-type cyclization was reported by Nakagawa and co-workers.<sup>[5]</sup> They described the ring closure of nitron **4** with up to 90% *ee* under the influence of a chiral borane (ca. 2 equiv) as a Lewis acid. Two examples of catalytic asymmetric Pictet–Spengler reactions have been reported recently: Taylor and Jacobsen described the cyclization of the *N*-acyliminium ion **5** with up to 95% *ee* under the catalysis of an enantiomerically pure thiourea,<sup>[6a]</sup> and List and co-workers disclosed the cyclization of the iminium diester **6** with up to 96% *ee* under the catalysis of an enantiomerically pure phosphoric acid derived from binaphthol.<sup>[6b]</sup> Although both methods are impressive examples of the power of asymmetric organocatalysis, the former has the disadvantage that the *N*-acetyl group is difficult to remove, and the latter is clearly limited in scope by the requirement of two ester functionalities.

Within our research program on the development of asymmetric reactions of iminium ions catalyzed by chiral Brønsted acids, we considered the use of *N*-sulfinyliminium ions as intermediates in the Pictet–Spengler condensation.<sup>[7]</sup> The sulfinyl substituent was expected to stabilize the intermediate iminium ion and thus favor Pictet–Spengler cyclization over undesired enamine formation.<sup>[8]</sup> Another advantage of the sulfinyl group is that its ready removal after the cyclization is ensured. Herein, we demonstrate the powerful combination of chiral phosphoric acids and *N*-sulfinyl tryptamines as a useful method for catalytic asymmetric Pictet–Spengler reactions.

The use of phosphoric acids derived from binaphthol as chiral catalysts in asymmetric synthesis was shown recently by two Japanese research groups to be highly successful for the addition of carbon-centered nucleophiles to prochiral iminium intermediates.<sup>[9,10]</sup> We set out to use such chiral acids as catalysts for the generation in situ and cyclization of *N*-sulfinyliminium ions derived from tryptamine.

The Pictet–Spengler precursors **7** and **8** were prepared readily by the treatment of tryptamine with the appropriate commercially available sulfinyl chlorides in the presence of a base. When the *N*-(*o*-nitrophenyl)sulfinyltryptamine **7** was

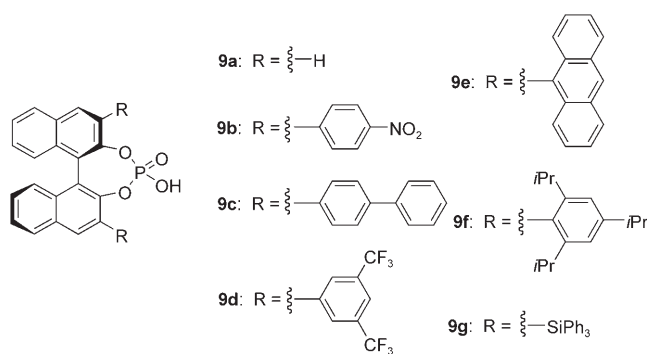


[\*] M. J. Wanner, Dr. R. N. S. van der Haas, K. R. de Cuba, Dr. J. H. van Maarseveen, Prof. Dr. H. Hiemstra  
Van't Hoff Institute for Molecular Sciences  
University of Amsterdam  
Nieuwe Achtergracht 129, 1018 WS Amsterdam (The Netherlands)  
Fax: (+31) 20-525-5670  
E-mail: hiemstra@science.uva.nl

[\*\*] This research was supported financially by the National Research School Combination Catalysis (NRSC-C). We thank R. Z. Boerleider and P. Hauwert for their help in the synthesis of the catalysts.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

stirred with *n*-hexanal (1.5 equiv) in chloroform in the presence of the (*R*)-binaphthylphosphoric acid **9a** (2 mol %)



at room temperature, the tetrahydro- $\beta$ -carboline **10** was obtained (Table 1). The reaction was attempted with a range of chiral phosphoric acid catalysts, **9b–9g**. In all cases excellent yields were observed (92–98 %), which underscores the power of *N*-sulphenyliminiums to facilitate Pictet–Spengler reactions. However, the enantioselectivities for the cyclization step were still unsatisfactory: In the best case, the use of catalyst **9d** led to **10** with a modest 31 % *ee*.

**Table 1:** Screening of catalysts for the asymmetric Pictet–Spengler reaction.

Catalyst	Substrate <b>7</b> <sup>[a]</sup> <i>t</i> [h] <sup>[c]</sup>	<b>10</b> : <i>ee</i> [%]	Substrate <b>8</b> <sup>[b]</sup> <i>t</i> [h] <sup>[c]</sup>	<b>11</b> : <i>ee</i> [%]
<b>9a</b>	1	5	1	–8
<b>9b</b>	1	12	4	41
<b>9c</b>	42	22	42	34
<b>9d</b>	1	31	2	88
<b>9e</b>	56	15	42	45
<b>9f</b>	56	4	20	74
<b>9g</b>	56	26	42	33

[a] Reaction conditions: **7** (0.10 mmol), *n*-hexanal (1.5 equiv), **9** (2 mol %), chloroform (1.0 mL), room temperature. [b] Reaction conditions: **8** (0.10 mmol), *n*-hexanal (3.0 equiv), **9** (5 mol %), BHT (5 mg), 3-Å MS (150 mg), toluene (1.0 mL), 0 °C. [c] The reaction was continued until > 95 % conversion. MS = molecular sieves.

We then turned our attention to the bulkier *N*-tritylsulphenyl-substituted tryptamine substrate **8**. The Pictet–Spengler reaction of **8** with *n*-hexanal required careful optimization. The *N*-tritylsulphenyltetrahydro- $\beta$ -carboline **11** appeared to be rather unstable, possibly as a result of homolytic cleavage of the trityl–sulfur bond. The addition of 3,5-di(*tert*-butyl)-4-hydroxytoluene (BHT) to the reaction mixture as a radical scavenger prevented the problems associated with the decomposition of the product. Further improvements included a solvent change from chloroform to toluene and a lowering of the reaction temperature to 0 °C. The use of even

lower temperatures had only a marginal effect on the enantioselectivity of the reaction. Importantly, the addition of powdered 3-Å molecular sieves to remove the water released during the formation of the iminium salt led to an improvement in both the yield and the enantioselectivity. The chiral Brønsted acids **9a–g** were screened under these optimized conditions. The best result was again obtained with catalyst **9d**, in the presence of which **11** was formed with a satisfactory 88 % *ee* (Table 1).

To avoid the isolation of the labile *N*-tritylsulphenyl product **11**, a one-pot procedure for the synthesis of the tetrahydro- $\beta$ -carboline **1a** was developed. Thus, the molecular sieves were removed by filtration after the completion of the reaction. First thiophenol (1.2 equiv) and then HCl (4 equiv) in dioxane (4M) were added to the filtrate, and the resulting mixture was stirred overnight to give the hydrochloride salt of the pure tetrahydro- $\beta$ -carboline as a precipitate. This salt was collected by filtration and then neutralized to provide pure **1a** in 87 % yield and with 84 % *ee* (Table 2). Comparison of the sign of the specific rotation of the product with literature

**Table 2:** Scope of the reaction with respect to the aldehyde substrate.<sup>[a]</sup>

Product	R	<i>t</i> [h]	Yield [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>
<b>1a</b>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	2	87	84
<b>1b</b>	CH(CH <sub>3</sub> ) <sub>2</sub>	24	77	78
<b>1c</b>	CH <sub>3</sub>	1	88	30
<b>1d</b> <sup>[d]</sup>	Cyclohexyl	24	81	72
<b>1e</b>	CH <sub>2</sub> CH <sub>2</sub> Ph	0.5	88	76
<b>1f</b>	Ph	4	90	87
<b>1g</b> <sup>[d]</sup>	Ph	24	77	82
<b>1h</b> <sup>[d]</sup>	4-NO <sub>2</sub> -Ph	24	78	82

[a] Reaction conditions: **8** (0.10 mmol), aldehyde (3.0 equiv), **9d** (5 mol %), BHT (5 mg), powdered 3-Å MS (150 mg), toluene (1 mL). [b] Yield of the isolated product after two steps. [c] Determined by <sup>1</sup>H NMR spectroscopy with (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol.<sup>[11]</sup> [d] **9d**: 10 mol %.

data<sup>[3]</sup> indicated that (*S*)-**1a** was formed as the major enantiomer when (*R*)-**9d** was used as the catalyst.

Next, the scope of the reaction with respect to the aldehyde substrate was investigated. Fast reactions with fair enantioselectivities occurred with  $\alpha$ -unbranched aldehydes, except in the case of acetaldehyde (Table 2). The best result was obtained with phenylacetaldehyde, the reaction of which led to the  $\beta$ -carboline **1f** in 90 % yield and with 87 % *ee*. The

aromatic aldehydes tested reacted more slowly; nevertheless, the corresponding products **1g** and **1h** were furnished in satisfactory yields and with satisfactory *ee* values.

As an indication of the scalability of the procedure, **1a** was formed with the same *ee* value of 84% and in comparable yield when the reaction was carried out on a 3-g scale. When the catalyst loading was lowered to 1.0 mol%, the Pictet–Spengler reaction still gave **1a** with 84% *ee*, but took 18 h to reach completion.

In conclusion, an efficient catalytic asymmetric synthesis of tetrahydro- $\beta$ -carboline<sup>[12]</sup> has been developed on the basis of the Pictet–Spengler condensation of *N*-sulfonyltryptamines with a wide range of aldehydes. The ease of both the introduction of the sulfonyl substituent and its acid-mediated removal make this method attractive. Present studies are directed towards the improvement of the enantioselectivity of the reaction by further fine-tuning of the sulfonyl substituent and chiral phosphoric acid catalyst.

Received: April 24, 2007

Published online: August 14, 2007

**Keywords:** asymmetric catalysis · chiral phosphoric acids · enantioselectivity · Pictet–Spengler reaction · sulfenamides

- [1] a) A. Pictet, T. Spengler, *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030–2036; b) G. J. Tatsui, *Pharm. Soc. Jpn.* **1928**, *48*, 453–459; c) E. D. Cox, J. M. Cook, *Chem. Rev.* **1995**, *95*, 1797–1842; d) T. Kaufmann in *New Methods in the Asymmetric Synthesis of Nitrogen Heterocycles* (Ed.: J. L. Vicario), Research SignPost, Trivandrum, India, **2005**, chap. 4, pp. 99–147.
- [2] For recent literature on biologically active tetrahydro- $\beta$ -carboline, see a) K. Gudmundsson, WO 2007002051, **2007**; b) W. Jiang, J. Guan, M. J. Macielag, S. Zhang, Y. Qiu, P. Kraft, S. Bhattacharjee, T. M. John, D. Haynes-Johnson, S. Lundeen, Z. Sui, *J. Med. Chem.* **2005**, *48*, 2126–2133; c) W. Wang, Z.-J. Ni, P. Barsanti, S. Pecchi, Y. Xia, N. Brammeier, N. Treutle, E. Jazan, K. Wayman, D. Dibble, J.-K. Cheng, WO 2005070930, **2005**.
- [3] G. Schmidt, H. Waldmann, H. Henke, M. Burkard, *Chem. Eur. J.* **1996**, *2*, 1566–1571.
- [4] C. Gremmen, B. Willemse, M. J. Wanner, G.-J. Koomen, *Org. Lett.* **2000**, *2*, 1955–1958.
- [5] H. Yamada, T. Kawate, M. Matsumizu, A. Nishida, K. Yamaguchi, M. Nakagawa, *J. Org. Chem.* **1998**, *63*, 6348–6354.
- [6] a) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559; b) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086–1087.
- [7] The use of *N*-sulfonyl substituents as protecting groups is known in peptide synthesis; see a) L. Zervas, D. Borovas, E. Gazis, *J. Am. Chem. Soc.* **1963**, *85*, 3660–3666; for reviews on sulfenamide chemistry, see b) F. A. Davis, U. K. Nadir, *Org. Prep. Proced. Int.* **1979**, *11*, 33–51; c) L. Craine, M. Raban, *Chem. Rev.* **1989**, *89*, 689–712; d) I. V. Koval, *Russ. Chem. Rev.* **1996**, *65*, 452–473.
- [8] List and co-workers showed that the treatment of tryptamine with propionaldehyde and substoichiometric trifluoroacetic acid leads to the formation of aldol-condensation products (see Ref. [6b]).
- [9] a) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357; b) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592–1594; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568.
- [10] For recent reviews on catalysis by chiral Brønsted acids, see a) S. J. Connon, *Angew. Chem. Int. Ed.* **2006**, *45*, 3909–3912; b) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999–1010; c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543.
- [11] a) M. S. C. Pedras, M. Hossain, M. G. Sarwar, S. Montaut, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5469–5471; b) W. H. Pirkle, D. J. Hoover, *Top. Stereochem.* **1982**, *13*, 263–331.
- [12] The extension of this method with *N*-sulfonyliminium ions to isoquinoline synthesis is presently under investigation.