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Enantioselective BINOL-Phosphoric Acid Catalyzed Pictet−Spengler Reactions of *N*-Benzyltryptamine

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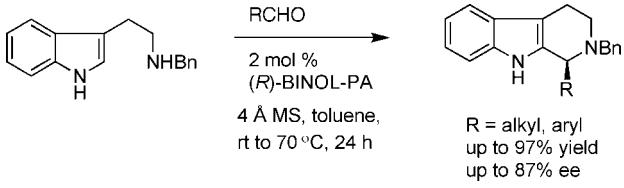


Optically active tetrahydro-β-carbolines were synthesized via an (*R*)-BINOL-phosphoric acid-catalyzed asymmetric Pictet−Spengler reaction of *N*-benzyltryptamine with a series of aromatic and aliphatic aldehydes. The tetrahydro-β-carbolines were obtained in yields ranging from 77% to 97% and with ee values up to 87%. The triphenylsilyl-substituted BINOL-phosphoric acid proved to be the catalyst of choice for the reaction with aromatic aldehydes. For the aliphatic aldehydes, 3,5-bistrifluoromethylphenyl-substituted BINOL-phosphoric acid was identified as the best catalyst.

Compounds containing the tetrahydro-β-carboline core (**1**) are of great interest because of their inherent biological activity.[1−3] Tetrahydro-β-carbolines are generally obtained via the Pictet−Spengler reaction of tryptamine with a variety of aromatic and aliphatic aldehydes in the presence of a Brønsted acid (Scheme 1).[4]

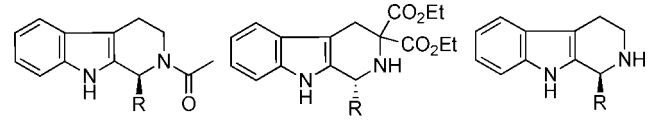
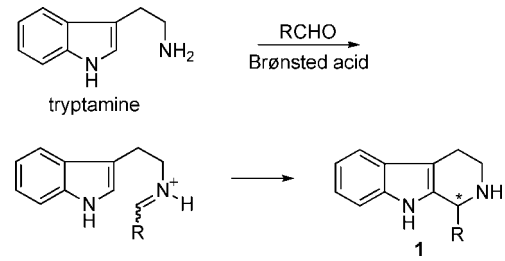


FIGURE 1. Tetrahydro-β-carbolines obtained via organocatalytic asymmetric Pictet−Spengler reactions.

SCHEME 1. Pictet−Spengler Reaction



Various stereoselective Pictet−Spengler reactions have been described of which especially Cook's approach using tryptophan esters as chiral precursors is noteworthy.[4b] However, the ester functionality had to be removed in a multistep sequence. Recently, an organocatalytic approach toward enantioenriched tetrahydro-β-carbolines (e.g., **2** in Figure 1) was developed mediated by a chiral thiourea catalyst (5−10 mol % catalyst, 65−81% yield, and 85−93% ee).[5] This reaction appeared to be limited to aliphatic aldehydes and, in addition, *N*-acetyl group removal proved to be difficult.

List and co-workers developed an asymmetric Pictet−Spengler cyclization of an iminium diester that provided tetrahydro-β-carbolines **3** in 40−96% yield and 62−96% ee with triisopropylphenyl-substituted (*S*)-BINOL phosphoric acid (20 mol %) as the catalyst.[6] Although both aromatic and aliphatic aldehydes were accepted in this reaction, the method required the presence of two ester functionalities and is therefore of limited utility.

Within our research program on the development of asymmetric reactions of iminium ions catalyzed by chiral Brønsted acids,[7] we recently reported a catalytic asymmetric Pictet−Spengler reaction via an *N*-sulfenyliminium ion catalyzed by a bis-trifluoromethylphenyl-substituted (*R*)-BINOL phosphoric acid (5−10 mol %). Both alkyl- and aryl-substituted tetrahydro-β-carbolines **4** were obtained in 77−90% yield in two steps (cyclization and removal of the tritylsulfenyl group in a one-pot procedure) with ee values up to 87%.[8]

† X-Ray crystal structure determination: Institute for Molecules and Materials, Radboud University, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands.

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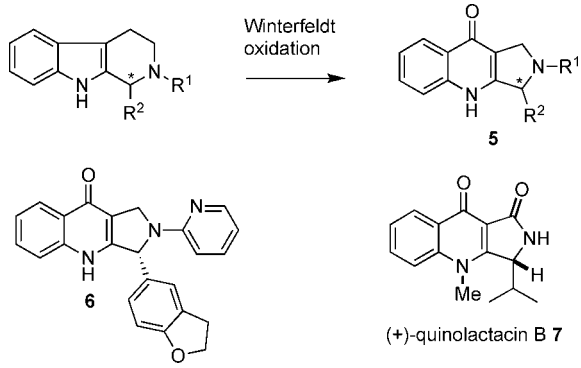
SCHEME 2. Winterfeldt Oxidation and Known Pyrroloquinolone Derivatives



N-Substituted tetrahydro-β-carbolines are the starting materials of choice for the pharmaceutically relevant pyrroloquinolones **5** via the Winterfeldt oxidation.[9]

Pyrroloquinolones (e.g., **6** in Scheme 2) are selective phosphodiesterase 5 (PDE5) inhibitors,[10] and the related quinolactacins such as **7** are known to play a key role in apoptosis.[11,12] Pyrroloquinolone **6**[10h] was proven to be superior in selectivity and potency in the treatment of male erectile dysfunction compared to the nowadays commercially available Viagra (sildenafil),[13] Levitra (vardenafil),[14] and Cialis (tadalafil).[15] Pyrroloquinolones such as **6** have been synthesized via an asymmetric Pictet−Spengler reaction from tryptamine functionalized with 1-naphthalen-1-yl-ethylamine as the chiral auxiliary.[10a] Starting from tryptophan a diastereoselective Pictet−Spengler reaction was achieved and the ester group was removed in 4 steps.[10h] Another route starts with (one pot) consecutive imine formation from tryptamine in boiling toluene, followed by an acid-catalyzed Pictet−Spengler cyclization and resolution with a chiral acid to afford the tetrahydro-β-carboline intermediate with high optical purity. After installing the *N*-benzyl the stage was set for the Winterfeldt oxidation.[10e,g]

Because *N*-benzyl-protected tetrahydro-β-carbolines are the most commonly used substrates for the Winterfeldt oxidation we herein report an asymmetric organocatalytic Pictet−Spengler reaction directly starting from *N*-benzyltryptamine.

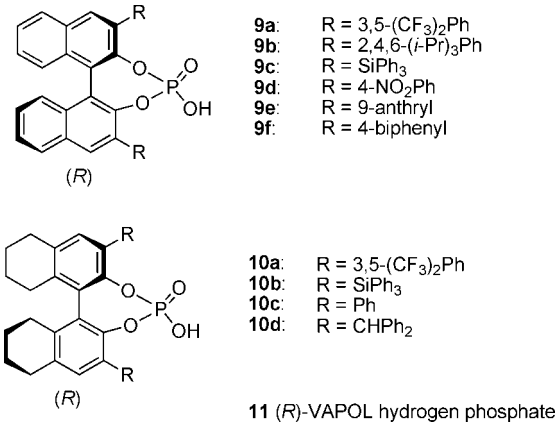
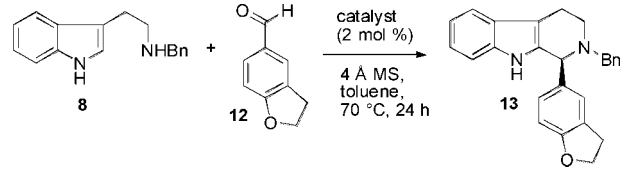


FIGURE 2. Chiral phosphoric acids.

TABLE 1. Catalyst Screening[a]



entry	catalyst	conversion (%)[b]	ee (%)[c]
1	**9a**	92	43
2	**9b**	62	49
3	**9c**	**100**	**85**
4	**9d**	76	35
5	**9e**	50	28
6	**9f**	40	10
7	**10a**	93	48
8	**10b**	90	78
9	**10c**	56	10
10	**10d**	93	19
11	**11**	28	15

[a] Reaction was conducted with **8** (0.05 mmol), **12** (3 equiv), and powdered 4 Å MS (75 mg) in toluene (0.5 mL) with 2 mol % catalyst at 70 °C for 24 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC on a chiral column (Chiralcel OD).

As 2,3-dihydrobenzofuran-5-carboxaldehyde **12** is employed in the synthesis of PDE5 inhibitors,[10] we have chosen this particular aldehyde to study the enantioselective Pictet−Spengler reaction starting from *N*-benzyltryptamine **8** providing tetrahydro-β-carboline **13**. A series of enantiopure phosphoric acid catalysts were screened (see Figure 2) and the results are listed in Table 1.

Low ee values were obtained with the binol phosphoric acids **9a**−**f**, except when triphenylsilyl catalyst **9c** was used (Table 1, entry 3). The H_8-BINOL phosphoric acids **10a** and **10b** gave almost full conversions and similar ee values as the related BINOL phosphoric acids. VAPOL hydrogen phosphate **11** proved to be unsuitable for this reaction as only low conversion and enantioselectivity were obtained.

With catalyst **9c** giving the best result, we then investigated the influence of catalyst loading and reaction temperature for this catalyst. In the absence of catalyst, it appeared that **13** was formed as a racemic mixture in a yield of 23−35% after 24 h (as observed in three different experiments).[16] Increasing the amount of catalyst to 5 mol % gave full conversion after 13 h

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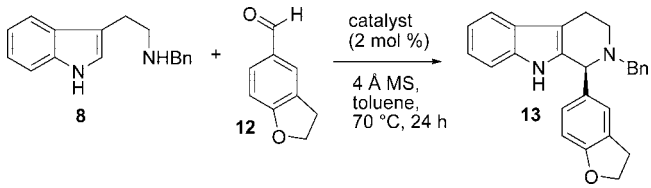
TABLE 2. Solvent and Additive Screening[a]



entry	solvent	additive	conversion[b]	ee (%)[c]
1	toluene		incomplete	41
2	xylenes	4 Å MS	full	79
3	C_6H_6	4 Å MS	full	79
4	DCE	4 Å MS	incomplete	57
5[d]	MeCN	4 Å MS	incomplete	35
6	toluene	3 Å MS	full	76
7	**toluene**	**4 Å MS**	**full**	**85**
8	toluene	5 Å MS	full	79
9	toluene	Na_2SO_4	incomplete	67

[a] Reaction was conducted with **8** (0.05 mmol), **12** (3 equiv), and drying agent (75 mg) in 0.5 mL of solvent with 2 mol % **9c** at 70 °C for 24 h. [b] Reaction monitored by TLC. [c] Determined by HPLC on a chiral column (Chiralcel OD). [d] Stirred for 48 h.

and **13** was obtained with an ee of 85%. With 10 mol % catalyst the reaction was complete in 4 h and afforded **13** with essentially the same ee (86%) as obtained with a catalyst loading of 2 or 5 mol % (see also Table 1). The best results in terms of ee were obtained at a temperature of 70 °C; at 50 °C the reaction of **8** with **12** was complete in 48 h (81% ee) and at 90 °C full conversion was observed after 12 h (82% ee) with a catalyst loading of 2 mol %.

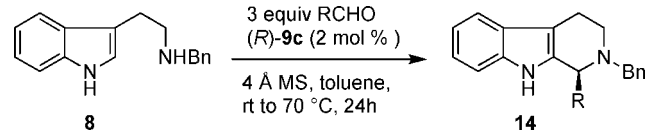
The study of the effects of solvent and additives is summarized in Table 2. The reaction proceeded at best in aromatic solvents with a clear preference for toluene. In the absence of mol sieves, the reaction was incomplete after 24 h and the product was obtained with a modest ee only (41%). A comparable result was obtained by using sodium sulfate as the drying agent. Slightly lower ee values were obtained when 3 Å and 5 Å MS were employed as compared to 4 Å MS. Possibly, water is able to break up the tight complex between the BINOL-phosphate and the cyclization precursor.

In our final optimization experiments, the stability of the Pictet−Spengler product was examined. We exposed enantiopure (*S*)-**13** to the reaction conditions (2 mol % of **9c**, 2 equiv of **13**, 4 Å MS, toluene, 70 °C, 24 h) and no racemization was observed. By application of the same reaction conditions to the racemic product **13** no enantiomeric enrichment was observed thus suggesting that the BINOL-phosphoric acid catalyzed Pictet−Spengler reaction of *N*-benzyltryptamine with **12** is irreversible under our reaction conditions.

With the optimal reaction conditions identified, we investigated the reaction with a series of aliphatic and aromatic aldehydes. The results are presented in Table 3.

All reactions proceeded smoothly to give the corresponding products **13** and **14** in good to high yields (77−97%). Both aromatic (bearing electron donating and electron withdrawing groups) and aliphatic aldehydes are tolerated. Moderate to good ee values were obtained in the range of 61−87%, with the best result with *p*-nitrobenzaldehyde (Table 3, entry 2). Remarkably, low ee values (0−20%) were obtained with *m*-chlorobenzaldehyde and with 3,5-bis(trifluoromethyl)benz-aldehyde (entries 4 and 5). The reason for the low ee in these two cases is unclear. Of the aliphatic aldehydes tested, 3-phenylpropanal (entry 16) gave the lowest ee and with the easy enolizable phenylacetaldehyde no product could be obtained (entry 15).

TABLE 3. Scope of the Reaction[a]



entry	R	product	yield (%)[b]	ee (%)[c]
1	*p*-BrC_6H_5	**14a**	92	85[d]
2[e]	*p*-$NO_2C_6H_5$	**14b**	95	87[f]
3	*p*-$CF_3C_6H_5$	**14c**	97	83[d]
4	*m*-ClC_6H_5	**14d**	92	20[g]
5	3,5-$(CF_3)_2C_6H_4$	**14e**	82	rac[g]
6	furfuryl	**14f**	84	80[d,h]
7[e]	piperonyl	**14g**	92	82[g]
8	dihydrobenzofuryl	**13**	80	85[d]
9	*p*-$MeOC_6H_5$	**14h**	84	80[g]
10[e]	3,4,5-$(OMe)_3C_6H_2$	**14i**	88	74[f]
11	C_6H_5	**14j**	95	72[g]
12	2,4-$Me_2C_6H_5$	**14k**	83	61[g]
13[i]	*i*-Pr	**14l**	90	81[g]
14[i]	*n*-pentyl	**14m**	77	68[g]
15[i]	benzyl	**14n**	0	
16[i]	2-phenylethyl	**14o**	93	8[g]

[a] Reaction was conducted with **8** (0.2 mmol), aldehyde (3 equiv), and powdered 4 Å MS (300 mg) in 2 mL of toluene with 2 mol % of **9c** at 70 °C for 24 h unless otherwise stated. [b] Isolated yield. [c] Determined by HPLC on a chiral column. [d] With Chiralcel OD. [e] 5 mol % of **9c** was used. [f] With Chiralpak AD. [g] With Chiralcel OD-H. [h] A different workup procedure was performed to prevent racemization, see the Supporting Information. [i] Reaction performed with catalyst **9a** (2 mol %) at room temperature.

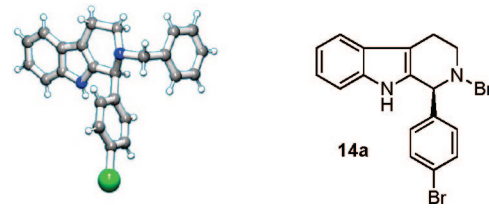


FIGURE 3. X-ray crystal structure of **14a**.

The Pictet−Spengler reactions with 2,3-dihydrobenzofuran-5-carboxaldehyde **12** and *p*-bromobenzaldehyde were also performed on a 1 mmol scale giving **13** and **14a** in similar yields and ee values. Both products were readily recrystallized to enantiomeric purity. From **14a** an X-ray crystallographic structure (Figure 3) was obtained revealing the absolute configuration which was found to be (*S*). This is in analogy with our previous results obtained for the Pictet−Spengler reaction with *N*-tritylsulfenyltryptamine.[8] The required biologically active (*R*)-enantiomer of benzofuran **13** was prepared with comparable yield and ee by using the corresponding (*S*)-triphenylsilyl-substituted BINOL catalyst **9c**.

In conclusion, we have developed an organocatalyzed asymmetric Pictet−Spengler reaction of *N*-benzyltryptamine (**8**) with a variety of aldehydes. Both aromatic and aliphatic aldehydes can be used in this reaction catalyzed by an enantiopure BINOL-derived phosphoric acid. The corresponding adducts are obtained in good to high yields and moderate to good ee values in one step. In addition, our scaleable method shortens the synthesis toward the pharmaceutically very relevant PDE5 inhibitors of the pyrroloquinolone class by three steps.

Experimental Section

(*S*)-2-Benzyl-1-dihydrobenzofuryl-1,2,3,4-tetrahydro-*β*-carboline (13). A mixture of *N*-benzyltryptamine (**8**, 250 mg, 1 mmol), 4 Å (powdered) molecular sieves (1.5 g), and catalyst **9c** (17.3 mg, 0.02 mmol) in 10 mL of toluene was stirred for 5 min at room temperature. Subsequently, 2,3-dihydrobenzofuran-5-carboxaldehyde (**12**, 178 mg, 1.2 mmol) was added and the mixture was stirred at 70 °C for 24 h under a nitrogen atmosphere. The reaction mixture was then cooled to room temperature and 3 g of silica gel was added followed by 5 mL of petroleum ether (PE). The resulting slurry was stirred for 5 min and filtered over a Celite path containing 2 g of silica gel (glass filter) and rinsed with 90 mL of eluent (PE:EtOAc = 5:1). Concentration of the filtrate afforded tetrahydro-*β*-carboline **13** in a yield of 69% (262.3 mg, 84% ee).

To obtain crystals the solid was dissolved in 0.5 mL of hot EtOAc and diluted with 1 to 2 mL of PE. The resulting solution was kept for 18 h in the refrigerator to give 35.3 mg (9% yield) of racemic crystals. The filtrate was concentrated to a small volume and diluted with PE (2 mL). After standing in the refrigerator for 18 h, 227 mg (60% yield, 96% ee) of solid was obtained. Recrystallization from EtOH gave enantiomerically pure (***S***)-**13** (99% ee determined by chiral HPLC on a Chiralcel OD column of heptane:isopropanol = 98:2, 0.8 mL/min, t_r major = 21.0 min, t_r minor = 24.3 min). Mp 167−168 °C. $[\alpha]^{22}_D$ +70 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.57−7.55 (m, 1H), 7.43−7.34 (m, 5H), 7.31−7.28 (m, 2H), 7.24−7.18 (m, 2H), 7.16−7.11 (m, 2H), 6.80 (d, J = 8.1 Hz, 1H), 4.62−4.58 (m, 3H), 3.98 (d, J = 13.6 Hz, 1H), 3.40 (d, J = 13.6 Hz, 1H), 3.30−3.24 (m, 1H), 3.23−3.13 (m, 2H), 2.99−2.92 (m, 1H), 2.85−2.80 (m, 1H), 2.73−2.68 (m, 1H); ^{13}C NMR (75.5 MHz; $CDCl_3$) δ 160.0, 139.5, 136.2, 135.3, 133.2, 128.9, 128.7, 128.2, 127.7, 127.2, 126.8, 125.4, 121.4, 119.3, 118.2, 110.7, 108.9, 108.8, 71.3, 64.1, 58.1, 48.4, 29.6, 21.2; IR (film) ν 3407, 3027, 2896, 2842, 2794, 1613, 1489; HRMS (FAB) *m*/*z* calcd for $[M + H]^+$ $C_{26}H_{25}N_2O$ 381.1967, found 381.1972.

(*S*)-2-Benzyl-1-(*p*-bromophenyl)-1,2,3,4-tetrahydro-*β*-carboline (14a). Compound **14a** was obtained in a yield of 92% (384.7 mg, 87% ee) following the procedure described for **13** with *p*-bromobenzaldehyde (222.0 mg, 1.2 mmol). Crystals were formed as described for (*S*)-**13** to give 41.2 mg (10% yield, 10% ee) of solid. The filtrate was concentrated to a small volume and diluted with PE (2 mL). After standing in the refrigerator for 18 h, 343.5 mg (82% yield, 98% ee) of solid was obtained. Recrystallization from EtOH gave enantiomerically pure (*S*)-**14a** (>99% ee determined on a Chiralcel OD column of heptane:isopropanol = 97:3, 1 mL/min, t_r major = 12.3 min, t_r minor = 16.4 min) which was used for X-ray crystal structure analysis. Mp 171−172.5 °C; $[\alpha]^{22}_D$ +67.4 (*c* 0.23, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.56−7.50 (m, 3H), 7.36−7.31 (m, 6H), 7.30−7.24 (m, 2H), 7.24−7.21 (m, 1H), 7.18−7.11 (m, 2H), 4.65 (s, 1H), 3.89 (d, J = 13.6 Hz, 1H), 3.42 (d, J = 13.6 Hz, 1H), 3.26−3.21 (m, 1H), 2.96−2.88 (m, 1H), 2.85−2.80 (m, 1H), 2.73−2.67 (m, 1H); ^{13}C NMR (75.5 MHz; $CDCl_3$) δ 140.7, 139.3, 136.4, 134.1, 131.9, 130.7, 128.7, 128.4, 127.2, 127.1, 122.0, 121.8, 119.5, 118.4, 110.9, 109.3, 63.7, 58.3, 48.1, 21.1; IR (NaCl) ν 3406, 2796, 1483; HRMS (FAB) *m*/*z* calcd. for $[M + H]^+$ $C_{24}H_{22}N_2Br$ 417.0966, found 417.0954.

Supporting Information Available: Analytical and spectral data, copies of ^{1}H and ^{13}C NMR spectra, and chromatograms of the compounds in Table 3, as well as of the catalysts **10a** and **10b**, and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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