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# Highly Enantioselective Pictet–Spengler Reaction Catalyzed by SPINOL-Phosphoric Acids

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Chiral tetrahydro-β-carbolines represent an important class of heterocycles in organic chemistry. They are structural units in a variety of natural products and important pharmaceuticals (Figure 1)[1] and useful intermediates for constructing several drugs, such as tadalafil.[2] Consequently, efficient methods for the preparation of optically pure tetrahydro-β-carbolines are in great demand. Whereas diastereospecific Pictet–Spengler reactions are well-known, approaches to tetrahydro-β-carbolines by using catalytic enantioselective variants, which provide the optically active tetrahydro-β-carbolines in a straightforward manner, have been a long-standing challenge.[3]

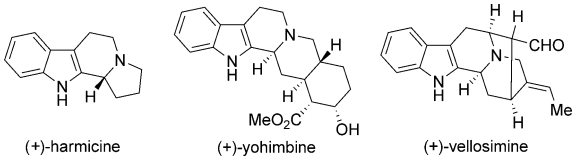


Figure 1. Alkaloids containing a tetrahydro-β-carboline unit.

Jacobsen et al. reported the first organocatalytic asymmetric Pictet–Spengler reaction of *N*-acyliminium ions by using a chiral thiourea catalyst (limited to aliphatic aldehydes, 5–10 mol% catalyst, 65–81% yield, and 85–93% *ee*).[3c] Recently, they also reported that chiral thiourea derivatives in combination with benzoic acid co-catalyze the asymmetric Pictet–Spengler reaction of electronically and sterically diverse imines, providing unprotected tetrahydro-β-carbolines in high yields and *ee* values.[3d] Since the pioneering work by Akiyama and Terada, BINOL-phosphoric acids have found widespread application as metal-free catalysts.[4] The first example of a BINOL-phosphoric acid catalyzed Pictet–Spengler reaction was reported by List et al., using a carboxy-substituted tryptophan as the key indole substrate (20 mol% catalyst, 40–96% yield, and 62–96% *ee*).[3e] Further applications with substrates, such as $N_b$-sulfenyliminium ions or $N_b$-benzyl tryptamine, were carried out by Hiemstra et al.[3f,g] and a *N*-acyliminium ion cyclization cascade was developed by Dixon et al.[3h] More recently, a BINOL-phosphoric acid catalyzed Pictet–Spengler reaction has also been employed in the natural product synthesis of (−)-arboricine[3i] as well as novel spiroindolinone compounds.[3j] Despite these elegant examples, general and efficient strategies for catalytic enantioselective protocols that tolerate a broad substrate scope with high enantioselectivity are in great demand.

Recently, we designed and synthesized a novel class of chiral SPINOL-phosphoric acids as Brønsted acids, which possess geometrically different and more rigid chiral parameters compared to the classic BINOL-phosphoric acids.[5] In our initial experiments, we found that these chiral SPINOL-phosphoric acids nicely promote the asymmetric Friedel–Crafts reaction of various indoles with a range of imines, giving comparable results to BINOL-phosphoric acids. List et al. independently reported a highly enantioselective kinetic resolution of homoaldols through a transacetalization reaction by using this novel class of chiral phosphoric acids.[6a] Lately, they reported a SPINOL-phosphoric acid catalyzed asymmetric Fischer indolization.[6b] Hu et al. also demonstrated that SPINOL-phosphoric acids give excellent enantioselectivities in the reaction of indoles with aldimines or β,γ-unsaturated-α-ketoesters.[7] More recently, Zhou et al. reported an asymmetric N−H insertion reaction, cooperatively catalyzed by Rhodium and SPINOL-phosphoric acids.[8] Herein, we would like to report the first example of a SPINOL-phosphoric acid catalyzed enantioselective Pictet–Spengler reaction.

Since $N_b$-protected tetrahydro-β-carbolines are key intermediates for the synthesis of biologically active pyrroloquinolones (e.g., tadalafil) through Winterfeldt oxidation, we carried out the organocatalytic Pictet–Spengler reaction starting directly from $N_b$-protected tryptamine. Thus, we selected the reaction between $N_b$-α-naphthylmethyl tryptamine (**3a**) and *p*-bromobenzaldehyde (**4a**) as a model reaction, using 2 mol% of catalyst in benzene at 30°C in the presence of powdered 4 Å molecular sieves. First, we investigated the influence of the catalyst and a series of chiral phosphoric acids was screened. As shown in Table 1, the sterically congested SPINOL-phosphoric acids were found to be crucial for a high activity and enantioselectivity. Interestingly, catalyst **1f**, which gave excellent enantioselectivities

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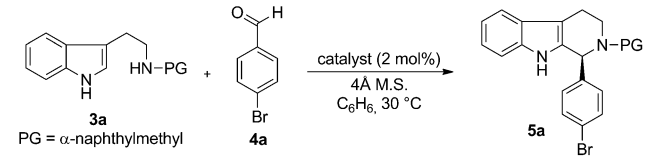
Table 1. Catalyst screening.[a]




| Entry | Catalyst | *t* [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 | **1a** | 48 | 72 | 87 |
| 2 | **1b** | 16 | 84 | 85 |
| 3 | **1c** | 24 | 80 | 78 |
| 4 | **1d** | 24 | 79 | 87 |
| 5 | **1e** | 8 | 99 | 96 |
| 6 | **1f** | 24 | 96 | 98 |
| 7 | **2a** | 24 | 70 | 79 |
| 8 | **2b** | 24 | 56 | 44 |

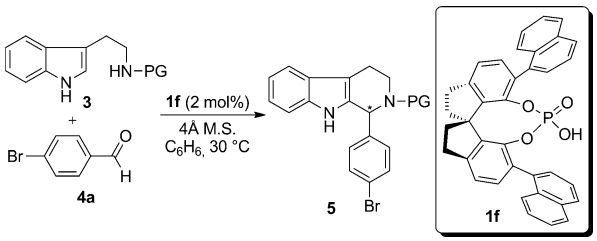
[a] Reaction conditions: catalyst (2 mol%), **3a** (0.1 mmol), **4a** (0.3 mmol), molecular sieves (4 Å, 0.15 g), benzene (1 mL), 30 °C. [b] Yield of the isolated, pure product. [c] The enantiomeric excess was determined by chiral HPLC analysis.

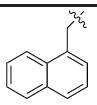
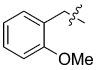
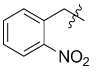
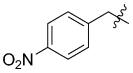
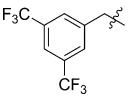
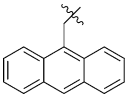
in our previous report,[5] also was the best catalyst for the present reaction, affording tetrahydro-β-carboline **5a** in 96% yield with 98% *ee* (Table 1, entry 6). However, BINOL-phosphoric acids **2a** and **b** gave low yields with poor enantioselectivities in this model reaction (Table 1, entries 7 and 8). These results demonstrate that SPINOL-phosphoric acids are highly efficient chiral organocatalysts, giving higher activities and enantioselectivities than the classic BINOL-phosphoric acids in some cases.

We envisioned that the yields and the *ee* values of tetrahydro-β-carbolines may be remarkably affected by the type of the $N_b$-protecting group of the tryptamine. Thus, a variety of $N_b$-protected tryptamines **3** were screened in the reaction with *p*-bromobenzaldehyde (**4a**) using 2 mol% of SPINOL-phosphoric acid **1f** as catalyst, and the results are summarized in Table 2. High yields were obtained, except when $N_b$-2-MeO-benzyl tryptamine (**3b**) and $N_b$-1-anthracen-9-ylmethyl tryptamine (**3g**) were used (Table 2, enties 2 and 7). High *ee* values were obtained with various $N_b$-protected tryptamines **3a–g**, and $N_b$-α-naphthylmethyl tryptamine (**3a**) gave the best enantioselectivity (Table 2, entry 1). In the case of $N_b$-benzyl tryptamine (**3f**), the classic BINOL-phosphoric acid **2b** gave poor activity and enantioselectivity (Table 2, entry 6). It is worth noting that the enantioselectivity could not be improved when the bulkier $N_b$-1-anthracen-9-ylmethyl tryptamine substrate (**3g**) was used (Table 2, entry 7).

We also examined different solvents, such as toluene, xylene, $CH_2Cl_2$, $ClCH_2CH_2Cl$, and THF (Table 3). In all cases, the reactions proceeded with good to excellent yields

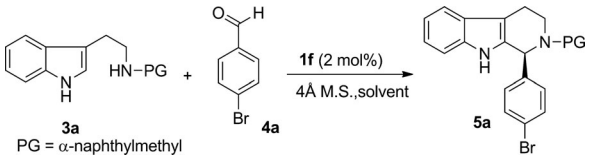
Table 2. Screening of the protecting group of tryptamine **3**.[a]




| Entry | Trypt-amine | PG | *t* [h] | Product | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | **3a** |  | 24 | **5a** | 96 | 98 |
| 2 | **3b** |  | 72 | **5b** | 35 | 91 |
| 3 | **3c** |  | 24 | **5c** | 98 | 90 |
| 4 | **3d** |  | 24 | **5d** | 93 | 90 |
| 5 | **3e** |  | 24 | **5e** | 90 | 92 |
| 6 | **3f** |  | 24 | **5f** | 90 (42)[d] | 93 (32)[d] |
| 7 | **3g** |  | 24 | **5g** | 63 | 95 |

[a] Reaction conditions: catalyst **1f** (2 mol%), **3** (0.1 mmol), **4a** (0.3 mmol), molecular sieves (4 Å, 0.15 g), benzene (1 mL), 30 °C. [b] Yield of the isolated, pure product. [c] The enantiomeric excess was determined by chiral HPLC analysis. [d] **2b** (2 mol%) was used.

Table 3. Optimization of the reaction conditions.[a]




| Entry | Solvent | *T* [°C] | *t* [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | benzene | 30 | 24 | 96 | 98 |
| 2 | toluene | 30 | 24 | 80 | 97 |
| 3 | xylene | 30 | 24 | 79 | 94 |
| 4 | $CH_2Cl_2$ | 30 | 8 | 95 | 91 |
| 5 | $ClCH_2CH_2Cl$ | 30 | 20 | 94 | 92 |
| 6 | THF | 30 | 16 | 94 | 94 |
| 7 | benzene | 23 | 48 | 81 | 95 |
| 8 | benzene | 40 | 12 | 98 | 95 |
| 9[d] | benzene | 30 | 42 | 92 | 96 |

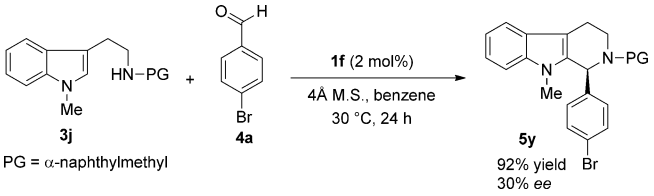
[a] Reaction conditions: catalyst **1f** (2 mol%), **3a** (0.1 mmol), **4a** (0.3 mmol), molecular sieves (4 Å, 0.15 g), benzene (1 mL), 30 °C. [b] Yield of the isolated, pure product. [c] The enantiomeric excess was determined by chiral HPLC analysis. [d] **1f** (1 mol%) was used.

and enantioselectivities, and benzene gave the best result (Table 3, entry 1). It was also found that increasing or lowering the temperature slightly reduced the enantioselectivity (Table 3, entries 7 and 8). Moreover, a decrease of the cata-

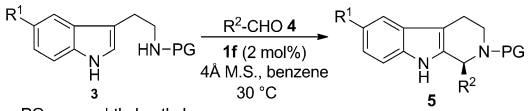
lyst loading (from 2 to 1 mol%) resulted in a slight drop of both the yield and the enantioselectivity (Table 3, entry 9).

With the optimized reaction conditions identified, we evaluated the substrate scope of the SPINOL-phosphoric acid catalyzed enantioselective Pictet–Spengler reaction of $N_b$-α-naphthylmethyl tryptamine with aldehydes. The representative results are summarized in Table 4. All reactions




Scheme 1. Pictet–Spengler reaction of tryptamine **3j** with aldehyde **4a**.

Table 4. Scope of the reaction.[a]




PG = α-naphthylmethyl
**3a**: $R^1$= H
**3h**: $R^1$= OMe
**3i**: $R^1$= Cl

| Entry | Tryptamine | $R^2$ (**4**) | *t* [h] | Product | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | **3a** | *p*-$BrC_6H_4$ (**4a**) | 24 | **5a** | 96 | 98 |
| 2 | **3a** | *m*-$BrC_6H_4$ (**4b**) | 12 | **5h** | 94 | 95 |
| 3 | **3a** | *m*-$ClC_6H_4$ (**4c**) | 12 | **5i** | 99 | 97 |
| 4 | **3a** | *m*-$FC_6H_4$ (**4d**) | 12 | **5j** | 97 | 97 |
| 5 | **3a** | *p*-$NO_2C_6H_4$ (**4e**) | 12 | **5k** | 99 | 96 |
| 6 | **3a** | *m*-$NO_2C_6H_4$ (**4f**) | 12 | **5l** | 99 | 94 |
| 7 | **3a** | 3,5-$(CF_3)_2C_6H_3$ (**4g**) | 16 | **5m** | 98 | 90 |
| 8 | **3a** | Ph (**4h**) | 30 | **5n** | 90 | 97 |
| 9[d] | **3a** | *p*-$MeOC_6H_4$ (**4i**) | 40 | **5o** | 94 | 95 |
| 10[d] | **3a** | piperonyl (**4j**) | 44 | **5p** | 95 | 92 |
| 11[d] | **3a** | dihydrobenzofuryl (**4k**) | 48 | **5q** | 91 | 93 |
| 12 | **3a** | furyl (**4l**) | 10 | **5r** | 92 | 98 |
| 13 | **3a** | Et (**4m**) | 4 | **5s** | 76 | 90 |
| 14 | **3a** | *n*-pentyl (**4n**) | 5 | **5t** | 98 | 91 |
| 15 | **3a** | *i*Pr (**4o**) | 5 | **5u** | 96 | 97 |
| 16 | **3a** | Cy (**4p**) | 6 | **5v** | 99 | 98 |
| 17 | **3h** | *i*Pr (**4o**) | 3 | **5w** | 96 | 95 |
| 18 | **3i** | *i*Pr (**4o**) | 12 | **5x** | 91 | 95 |

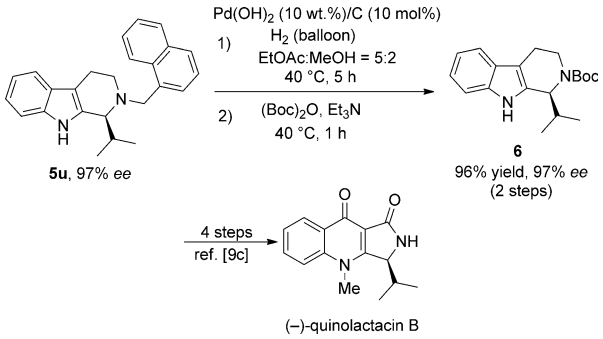
[a] Reaction conditions: **1f** (2 mol%), **3** (0.1 mmol), **4** (0.3 mmol), molecular sieves (4 Å, 0.15 g), benzene (1 mL), 30 °C. [b] Yield of the isolated, pure product. [c] The enantiomeric excess was determined by chiral HPLC analysis. [d] **1e** (2 mol%) was used instead of **1f**.

proceeded in good to excellent yields and with generally excellent enantioselectivities. It is worth noting that tetrahydro-β-carboline **5q** can be employed as a useful intermediate for the synthesis of PDE5 inhibitor tadalafil.[2] Furfuraldehyde also gave an exciting result (Table 4, entry 12). Importantly, a series of aliphatic aldehydes was examined and showed good tolerance (Table 4, entries 13–16, 76–99% yield, 90–98% *ee*). We also examined different tryptamines **3h** and **i** under the optimized conditions, which provided high yields and excellent *ee* values (Table 4, entries 17 and 18).

The absolute configuration of tetrahydro-β-carbolines **5a–x** was correlated to the absolute configuration of **5u**, which was confirmed to be *S* by comparing the optical rotation of its $N_b$-deprotected product with the literature (see the Supporting Information for details).

Moreover, tryptamine **3j** was examined as a substrate for the asymmetric Pictet–Spengler reaction under the optimized conditions. A remarkable decrease in enantioselectivity was observed, although an excellent yield was obtained (Scheme 1). This investigation indicates that the $N_a$–H bond of the tryptamine enhances the enantioselectivity. We believe that the bifunctional nature of the chiral phosphoric acid concurrently activates both the nucleophilic group and the electrophilic iminium intermediate, generated in situ through hydrogen-bonding interactions in the Pictet–Spengler reaction.

To extend the synthetic value of our approach, the deprotection of the tetrahydro-β-carboline products in a convenient way would be of great value (Scheme 2). To our delight, the α-naphthylmethyl group of **5u** was successfully removed



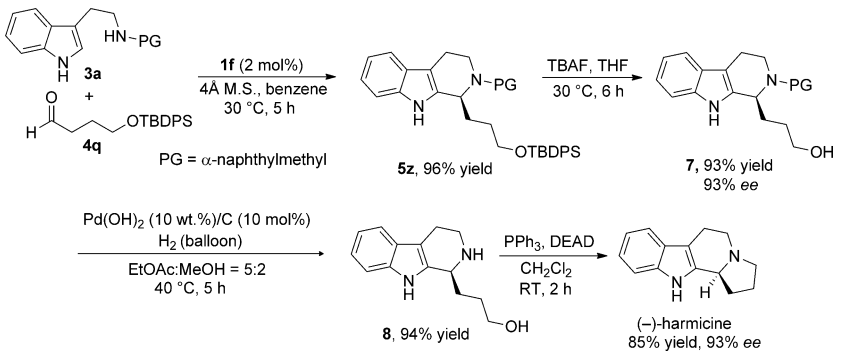

Scheme 2. Synthesis of terahydro-ß-carboline derivate **6**.

by using 10 mol% $Pd(OH)_2$ (10 wt%)/C as catalyst with a balloon of $H_2$ under mild reaction conditions. After treatement with $(Boc)_2O$, $N_b$-Boc-tetrahydro-β-carboline derivate **6**, which could be employed in Winterfeldt oxidation to obtain (−)-quinolactacin B,[9] was obtained in 96% yield with 97% *ee* over two steps.

This current protocol was also applied to the asymmetric total synthesis of (−)-harmicine (Scheme 3).[10] Initially, compound **5z** was readily prepared in 96% yield by treatment of tryptamine **3a** with aldehyde **4q** under the optimized reaction conditions. Subsequent deprotection of the TBDPS group afforded compound **7** in 93% yield with 93% *ee*, which was further deprotected under 1 atm $H_2$ to generate **8** in 94% yield. Finally, cyclization through Mitsunobu reaction led to the desired (−)-harmicine in 85% yield with 93% *ee*, and the total yield was 71% over four steps.

In conclusion, we have developed an efficient SPINOL-phosphoric acid catalyzed asymmetric Pictet–Spengler reac-




Scheme 3. Total synthesis of (−)-harmicine. TBDPS = *tert*-butyldiphenylsilyl, TBAF = tetra-*n*-butylammonium fluoride, DEAD = diethyl azodicarboxylate.

tion of $N_b$-α-naphthylmethyl tryptamines with a wide range of aliphatic and aromatic aldehydes, affording a series of highly enantioenriched tetrahydro-β-carboline derivatives in excellent yields and *ee* values. In addition, the utility of this method has been demonstrated in the preparation of the key intermediate of (−)-quinolactacin B and in the asymmetric total synthesis of (−)-harmicine. Applications of the current protocol in the total synthesis of other natural products are underway.

## Experimental Section

**General procedure for the enantioselective Pictet–Spengler reaction**: A mixture of $N_b$-α-naphthylmethyl tryptamine **3** (0.1 mmol), catalyst **1f** (0.002 mmol), and 4 Å molecular sieves (0.15 g, powdered) in benzene (1 mL) was stirred for 5 min at room temperature under a nitrogen atmosphere. Subsequently, aldehyde **4** (0.3 mmol) was added, and the mixture was stirred at 30 °C for the appropriate time. The reaction was monitored by TLC. After the reaction was complete, the reaction mixture was directly purified by flash column chromatography (eluent: ethyl acetate/petroleum ether 1:15→1:8 with 2% TEA) to give the desired product **5**.

## Acknowledgements

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**Keywords:** phosphoric acids · heterocycles · organocatalysis · Pictet–Spengler reaction · tryptamines

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