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Catalytic Asymmetric Pictet−Spengler Reaction

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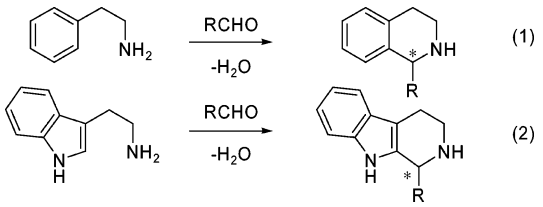
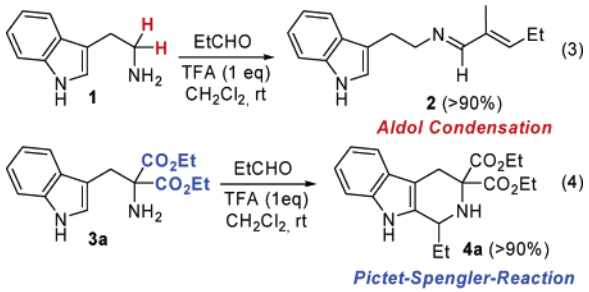
The Pictet−Spengler reaction[1] is an important acid-catalyzed transformation frequently used in the laboratory as well as by various organisms for the synthesis of tetrahydro-*β*-carbolines or tetrahydroisoquinolines from carbonyl compounds and phenyl ethylamines or tryptamines, respectively (eqs 1 and 2).[2]



Nature has evolved enzymes that catalyze the reaction enantioselectively, apparently even in humans.[3] However, despite its importance for alkaloid synthesis,[2] small-molecule catalysts of the asymmetric Pictet−Spengler reaction have been unknown. In addition to useful substrate- or auxiliary-controlled diasteroselective versions,[4] one enantioselective nitrone Pictet−Spengler reaction has been developed that requires superstoichiometric amounts of a chiral Lewis acid reagent.[5] Very recently, Jacobsen et al.[6] reported the first truly catalytic approach by developing an elegant organocatalytic acyl Pictet−Spengler reaction. *The direct Pictet−Spengler reaction of aldehydes with aryl ethylamines, however, has been an illusive target for small-molecule catalysis.* We now report an efficient and highly enantioselective Brønsted acid-catalyzed Pictet−Spengler reaction of substituted tryptamines to the corresponding tetrahydro-*β*-carbolines using a chiral phosphoric acid catalyst.

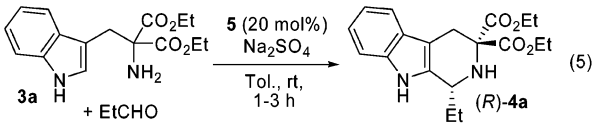
The reason for the hampered development of a catalytic asymmetric Pictet−Spengler reaction may be the requirement for rather strong Brønsted acid catalysts. This catalyst type, however, has not been considered for use in *asymmetric* catalysis for a long time. Only very recently, Akiyama et al.[7] and Terada et al.[8] demonstrated, in pioneering studies, that relatively strong chiral binaphthol-derived phosphoric acids are efficient and highly enantioselective catalysts for addition reactions to aldimines. We have very recently extended this concept to ketimines in highly enantioselective Brønsted acid-catalyzed transfer hydrogenations.[9] Since these reactions are assumed to involve chiral, hydrogen-bond-assisted iminium−phosphate ion pairs, we reasoned that the approach might be applicable to the Pictet−Spengler reaction, which also proceeds via iminium ion intermediates.

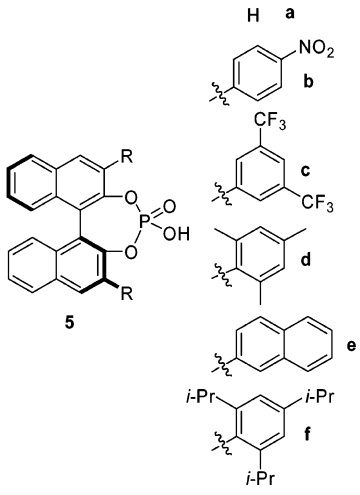
In line with observations by Jacobsen et al., attempts to carry out acid catalysis of the Pictet−Spengler reaction of simple standard substrates such as unsubstituted tryptamines and phenylethylamines proved unfruitful. For example, treating typtamine itself (**1a**) with propionaldehyde and trifluoroacetic acid (TFA) gave only compound **2**, resulting from homo-aldol condensation and imine formation (eq 3). We reasoned that one solution for this problem might be the use of more reactive substrates that are predisposed for cyclization. Specifically, we hypothesized that easily accessible geminally disubstituted tryptamines such as **3a**[10] are promising substrates for electronic reasons and might favor cyclization by virtue of a Thorpe−Ingold effect. Indeed, treatment of **3a** with TFA cleanly provided the desired product **4a** in high yield.



Encouraged by this result, we set up a study to identify a chiral organic Brønsted acid to be used as asymmetric catalyst. After screening several substituted chiral phosphoric acids (**5**),[11] we found catalyst **5f**, which we have previously used in our imine reduction, to give the highest enantioselectivity in the Pictet−Spengler reaction of tryptamine **3a** with propionaldehyde in the presence of Na_2SO_4 (Table 1).

Table 1. Catalyst Screening



Catalyst[a]	R	Yield[b] [%]	*ee*[c] [%]
	H **a**	91	5
	b	80	14
	c	95	18
	d	96	52
	e	75[d]	30
	f	90	66

5

[a] For additional catalysts studied, see the Supporting Information. [b] Determined by GC. [c] Determined by HPLC (Chiralcel OD-RH). Absolute configuration determined by hydrolytic decarboxylation to the monoester. [d] 24 h.

Reducing the reaction temperature to −30 °C further improved the enantiomeric excess (ee) of carboline derivative **4a** to 88% (eq 6, Table 2). We have investigated other tryptamines (**3b**−**d**) under the same reaction conditions and found that generally high yields

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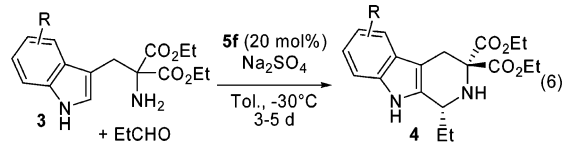
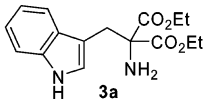
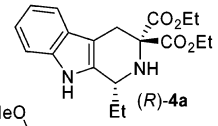
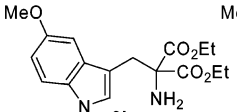
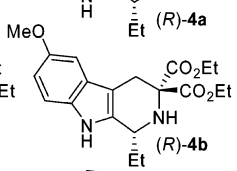
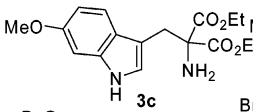
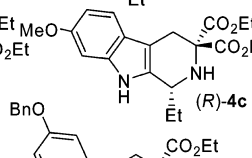
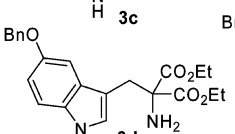
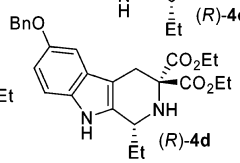
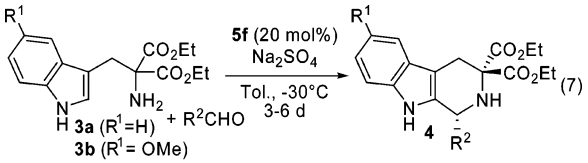
Table 2. Tryptamine Variations



Tryptamine	Product	Yield [%][a]	*ee* [%][b]
 **3a**	 (*R*)-**4a**	76	88
 **3b**	 (*R*)-**4b**	96	90
 **3c**	 (*R*)-**4c**	94	86[c]
 **3d**	 (*R*)-**4d**	98	90

[a] Isolated yield. [b] Determined by HPLC (Chiralcel OD-RH or Chiralpak AD-RH). [c] Using catalyst **5d**.

Table 3. Aldehyde Variations

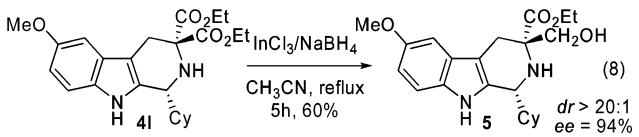


Entry	R^1	R^2	Yield [%][a]	*ee* [%][b]
1	OMe	Et	96	90
2	H	Et	76	88
3	OMe	*n*-Pr	98	88
4	OMe	*n*-Bu	90	87
5	H	*n*-Bu	91	87
6	OMe	*i*-Bu	96	80
7	OMe	Bn	85	72
8	H	Bn	58	76
9	OMe	*i*-Pr	85	81
10[c]	OMe	Cy	64	94
11	OMe	2-pentyl	50	84
12[d]	OMe	*p*-O_2N-C_6H_4	98	96
13[d]	H	*p*-O_2N-C_6H_4	60	88
14[d]	OMe	*p*-NC-C_6H_4	60	80
15[d]	H	*p*-NC-C_6H_4	40	89
16[d]	OMe	Ph	82	62

[a] Isolated yield. [b] Determined by HPLC (Chiralcel OD-RH or Chiralpak AD-RH). [c] At −45 °C (ee = 91%, yield = 93% at −30 °C). [d] At −10 °C in CH_2Cl_2.

(94−98%) and good ee's (86−90%) were obtained. Next, the aldehyde scope of the reaction was investigated using tryptamines **3a**,**b** (eq 7, Table 3). Remarkably, the reaction tolerates a variety of different aldehydes with good results. Accordingly, both aliphatic unbranched aldehydes (entries 1−8) and branched aldehydes (entries 9−11) gave the products in reasonable to excellent yields (50−98%) and in high ee's (72−94%). In contrast to the acyl Pictet−Spengler variant developed by Jacobsen et al., which does not tolerate aromatic aldehydes, our reaction works very well with these substrates, especially with electron-poor aromatic aldehydes, giving the carboline products in up to 98% yield and 96% ee (entries 12−16).

The requirement of a geminal diester functionality constitutes a current limitation of our methodology. However, the diester can also be of use for further transformations via diastereoselective functional group differentiation. For example, treatment of Pictet−Spengler product **4l** with $NaBH_4/InCl_3$ provided mono-alcohol **5** highly distereoselectively (eq 8).[12]



In summary, we have developed a catalytic asymmetric Pictet−Spengler reaction. Our process furnishes enantioenriched tetrahydro-β-carbolines from various tryptamines and both aromatic and aliphatic aldehydes if treated with chiral Brønsted acid catalyst **5f**. Further extensions and applications of this methodology are forthcoming.

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Supporting Information Available: Experimental procedures, compound characterization, NMR spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Phosphoric acids **5** were prepared according to or in analogy to the reported procedures; see refs 7, 8.
(12) For previous use of this reagent combination, see: Haldar, P.; Ray, J. K. *Org. Lett.* **2005**, *7*, 4341−4343.

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