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An Easy Entry to Optically Active Spiroindolinones: Chiral Brønsted Acid-Catalysed Pictet–Spengler Reactions of Isatins

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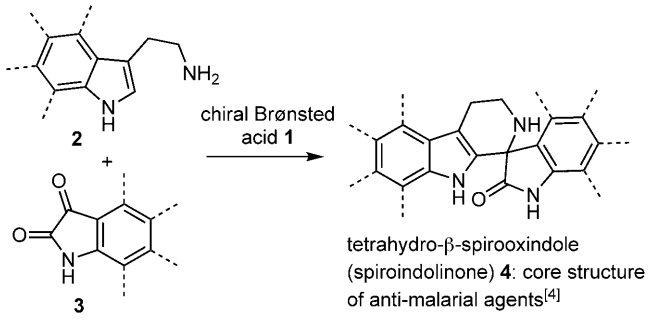
Abstract: The first catalytic asymmetric Pictet–Spengler reaction of isatins is presented. BINOL-derived phosphoric acids were found to be competent catalysts for this transformation, giving challenging spirooxindole structures bearing a quaternary stereocentre with generally good results. The 1,2,3,4-tetrahydro-β-carboline products (spiroindolinones) are the core of some newly discovered anti-malarial agents.

Keywords: asymmetric catalysis; Brønsted acids; organocatalysis; Pictet–Spengler reaction; spirooxindoles

Spirooxindole is a privileged scaffold in medicinal chemistry. Taking inspiration from bioactive compounds isolated from natural sources, many spirooxindole derivatives have been prepared in recent times. A number of these compounds shows outstanding biological profiles.[1] Some of these molecules are indeed very promising drug candidates for the treatment of, e.g., cancer,[2] tuberculosis,[3] and malaria.[4] However, the molecular and stereochemical complexity that identifies this class of compounds still represents a significant synthetic challenge.[1a–c,5] The construction of a highly hindered, strained spirocyclic quaternary chiral centre is in fact not a trivial task, especially in an enantioselective fashion.[6]

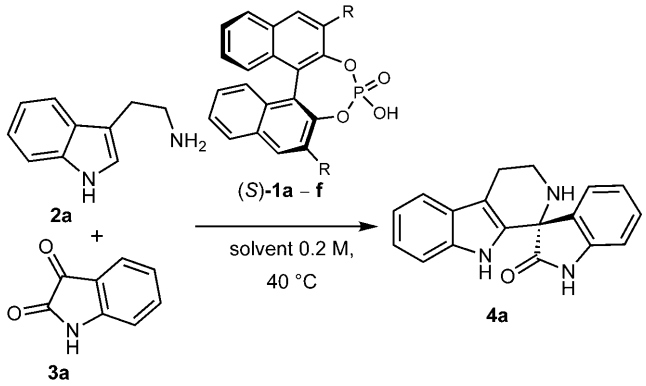
In the last years, catalytic asymmetric cycloaddition[7] and cascade[8] reactions have proved to be amongst the most powerful approaches for the direct enantioselective assembly of the spirooxindole framework, starting from commercial or readily available compounds. These reports are however mostly limited to pyrrolidin-3-yl-spirooxindole motives resembling the natural spirotryprostatins,[7] or to all-carbon cycloalkyl-spirooxindoles.[8a–d] We disclose herein a direct catalytic enantioselective access to tetrahydro-β-carboline spirooxindoles (spiroindolinones) **4**. These unique spirooxindole architectures are assembled by means of a chiral Brønsted acid[9]-catalysed Pictet–Spengler[10] reaction between tryptamines **2** and isatins **3** (Scheme 1), thus giving the first access to this class of compounds in an enantioselective manner. Remarkably, tetrahydro-β-carboline spirooxindoles of type **4** are the core of some potent anti-malarial agents showing very good pharmacokinetic properties, recently discovered by intensive high throughput screening processes.[4]

We started our optimisation (Table 1) by studying the reaction of tryptamine **2a** with isatin **3a** under the catalysis of several (*S*)-BINOL derived phosphoric acids **1a–f** with different substituents at the 3 and 3′ positions (Table 1 entries 1–6).[9,11] THF was chosen as reaction medium to ensure solubilisation of isatin **3a**. After 20 h at 40 °C, all reactions worked quite well from a conversion standpoint. However, all the Brønsted acids **1** tested furnished poor enantioselectivity with the only exception of **1f**[12] that allowed us



Scheme 1. Catalytic asymmetric Pictet–Spengler reaction between tryptamines **2** and isatins **3**.

Table 1. Optimisation of the reaction conditions for the asymmetric Pictet-Spengler reaction of tryptamine **2a** with isatin **3a**.[a]



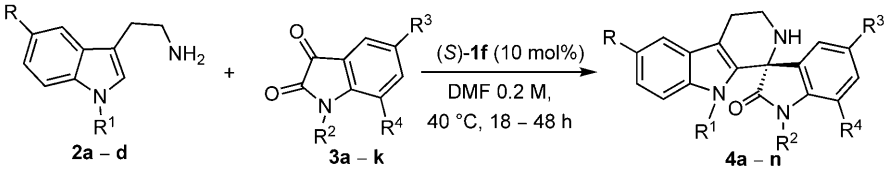
Entry	R	Solvent/$[\mathbf{2a}]_0$	Conv [%][b]	*ee* [%][c]
1	Ph (**1a**)	THF/0.2 M	64	<5
2	biphenyl (**1b**)	THF/0.2 M	56	<5
3	4-NO_2-C_6H_4 (**1c**)	THF/0.2 M	54	<5
4	$SiPh_3$ (**1d**)	THF/0.2 M	40	<5
5	3,5-$(CF_3)_2$-C_6H_3 (**1e**)	THF/0.2 M	58	40
6	2,4,6-(*i*-Pr)$_3$-C_6H_2 (**1f**)	THF/0.2 M	full	86
7[d]	**1f**	THF/0.2 M	50	90
8	**1f**	CH_2Cl_2/0.2 M	full	54
9	**1f**	MeCN/0.1 M	90	82
10	**1f**	EtOH/0.2 M	full	70
11	**1f**	DMF/0.2 M	full	92 (99)[e]
12	**1f**	DMF/0.5 M	89	90
13	**1f**	DMF/1.0 M	90	80
14	**1f**	DMF/0.1 M	full	92
15[f]	**1f**	DMF/0.2 M	full	88

[a] Unless otherwise specified, the reactions were performed at 40 °C on a 0.05 mmol scale (**2a**:**3a** = 1:1), using 10 mol% of catalyst.
[b] Determined by ^{1}H NMR analysis of the crude mixture, refers to both ketimine and isatin **3a**.
[c] Determined by HPLC analysis on chiral stationary phases.
[d] Reaction performed at room temperature for 65 h.
[e] After a single crystallisation.
[f] 5 mol% of (*S*)-**1f** was used.

to obtain the desired compound **4a** in 86% enantiomeric excess (Table 1, entry 6). The same reaction conducted at room temperature furnished slightly better enantiocontrol, yet careful analysis of the crude mixture revealed the presence of the ketimine intermediate even after 65 h (Table 1, entry 7). This observation prompted us to evaluate the feasibility of the reaction in other solvents (Table 1, entries 8–11).[13] We found that DMF was the solvent of choice with regard to reactivity and enantioselectivity. The reaction proceeded smoothly in this medium affording product **4a** in 92% *ee* (Table 1, entry 11). To additionally optimise the reaction conditions, the use of some additives was explored, without finding any beneficial effect.[13] The reaction revealed to be negatively influenced also by an increase in reagent concentration, although a more diluted solution did not affect the stereochemical outcome (Table 1, entries 11–14). Decreasing catalyst loading to 5 mol% gave slightly diminished enantioselectivity (Table 1, entry 15). Worthy of note is that essentially enantiopure **4a** could be obtained after a single crystallisation (Table 1, entry 11).

With optimal conditions at hand we focussed our attention on the scope of the reaction between various tryptamines **2a–d** and isatins **3a–k** for the synthesis of enantioenriched spiroindolinones **4a–n** (Table 2). Variation of the isatin **3** structure was very well tolerated by the catalytic system. Different isatins **3a–g**, bearing substituents with different electronic or steric properties at the various positions of the aryl ring, all gave the corresponding adducts **4a–g** with good results in terms of yields and enantioselectivities (Table 2, entries 1–7). Substitution with differ-

Table 2. Brønsted acid-catalysed Pictet–Spengler reaction of tryptamines **2a–d** with isatins **3a–k**.[a]



Entry	**2**	R	R^1	**3**	R^2	R^3	R^4	**4** Yield [%][b]	*ee* [%][c]
1	**2a**	H	H	**3a**	H	H	H	**4a** 85	92
2	**2a**	H	H	**3b**	H	F	H	**4b** 87	89
3	**2a**	H	H	**3c**	H	H	F	**4c** 80	90[d]
4	**2a**	H	H	**3d**	H	H	Cl	**4d** 80	90[d]
5	**2a**	H	H	**3e**	H	Me	Me	**4e** 81	76
6	**2a**	H	H	**3f**	H	MeO	H	**4f** 75	90
7	**2a**	H	H	**3g**	H	Me	H	**4g** 81	84
8	**2a**	H	H	**3h**	Me	H	H	**4h** 74	95
9	**2a**	H	H	**3i**	All	H	H	**4i** 80	92[d]
10	**2a**	H	H	**3j**	Bn	H	H	**4j** 68	73[d]
11	**2a**	H	H	**3k**	Me	Me	H	**4k** 97	90[d]
12[e]	**2b**	Br	H	**3h**	Me	H	H	**4l** 90	78[d]
13	**2b**	MeO	H	**3a**	H	H	H	**4m** 87	90
14	**2d**	H	Me	**3a**	H	H	H	**4n** 74	71

[a] Unless otherwise specified, the reactions were performed at 40 °C on a 0.1 mmol scale (**2**:**3** = 1:1) with 10 mol% of (*S*)-**1f**. Reaction time 18–48 h.
[b] Isolated yield after chromatography on silica gel.
[c] Determined by HPLC analysis on chiral stationary phases.
[d] Refers to the opposite enantiomer. (*R*)-**1f** was used as the catalyst.
[e] Reaction performed at 60 °C.

ent groups at the isatin nitrogen was also possible. An effect of the steric hindrance of this substituent was however observed, as the relatively small methyl and allyl groups in isatins **3h**, **i**, **k** gave the corresponding adducts **4h**, **i**, **k** with comparable, or even better, results than the parent unsubstituted isatin **3a**, whereas with the more hindered 1-benzyl isatin **3j** a decrease in the enantioselectivity was observed (Table 2, entries 8–11). Variation of tryptamine structure was then explored, indicating the possibility of using indoles differently substituted at the 5-position, such as the serotonine derivative **2c** and the corresponding bromo derivative **2b** (Table 2, entries 12 and 13). The requirement of a higher reaction temperature (60 °C) for the latter less reactive bromo derivative **2b** caused a slight decrease in stereoselctivity. Tryptamine **2d** bearing a methyl substituent at the indole nitrogen could also be employed (Table 2, entry 14).

The absolute configuration of compound **4a** was determined as *S* by simulation of the electronic circular dichroism spectra (ECD) and $[\alpha]_D$ values.[13] In many organocatalytic asymmetric processes involving the indole nucleus, coordination of the indole NH by a Lewis base moiety is considered to be crucial for reactivity and enantioselectivity.[14] However, in this asymmetric Pictet–Spengler reaction, the corresponding *N*-methylindole tryptamine **2d** gave similar, albeit lower, enantioselectivity (71% *ee vs.* 92% *ee*), with same *Si*-face selectivity.[15] Also in this case, the absolute configuration of **4n** was determined from its ECD spectrum.[13] This result might suggest that a Lewis base interaction with the indole N–H is not operative. An eventual interaction between the Lewis base moiety of the catalyst (P=O) with the proton at the 2-position of the indole nucleus might instead be envisioned, assisting the hydrogen transfer process,[16] resulting in the transition state depicted in Figure 1. Steric constraints and bi-coordination of the (*S*)-BINOL-derived catalyst **1f** force the activated ketimine into the conformation shown, thus giving addition at the *Si*-face. A possible interaction with the isatin NH can instead be excluded, given the very similar behaviour of isatins **3h–k**, bearing different alkyl substituents at nitrogen, with the parent isatin **3a**.

Finally, the surprising tolerance of this reaction to small amounts of water is remarkable and deserves some comments. During the optimisation process,[13] the same results in terms of catalyst activity and selectivity were in fact observed with reagent grade or dry solvents, with or without different desiccants (i.e., molecular sieves), in sharp contrast with most phosphoric acid **1**-catalyzed asymmetric transformations.[9,10,12,15,17] Even more striking, the addition of increasing quantities of water to the mixture did not compromise the

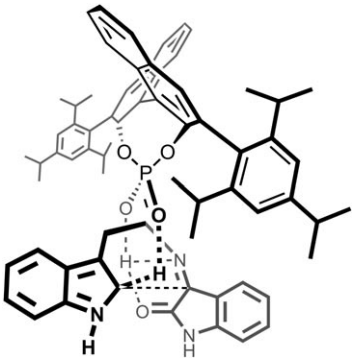


Figure 1. Proposed transition state.

enantioselectivity, although conversion was lowered. The high polarity of the optimum solvent (DMF), able in principle to accept hydrogen bonds, is also noteworthy. Taken together, these data highlight the unique properties of the large tris(isopropyl)phenyl substituents of catalyst **1f**, which have recently allowed the development of the first asymmetric phosphoric acid-catalyzed reaction in water.[18] A possible interpretation ascribes to the hindered aryl groups of phosphoric acid **1f** the ability to wrap the active site of the catalyst in a hydrophobic pocket, "protecting" the ketimine complex depicted in Figure 1 from external hydrogen bond donors or acceptors.

In summary, the first catalytic asymmetric Pictet–Spengler reaction using isatins as carbonyl components was developed, giving easy access to optically active spiroindolinones starting from readily available catalysts and starting materials. The tolerance to moisture gives a further practical dimension to this transformation, which furnishes enantioenriched structures of great interest for their biological properties, being the core of some newly discovered antimalarial agents.

Experimental Section

General Procedure

To a test-tube equipped with a magnetic stirring bar were sequentially added the tryptamine **2a–d** (0.10 mmol), catalyst (*S*)-**1f** (7.5 mg, 0.010 mmol, 10 mol%), DMF (reagent grade, 500 μL) and the isatin **3a–k** (0.10 mmol). The test-tube was capped and placed in an oil bath at 40 °C. The mixture was then vigorously stirred at the same temperature for 18–48 h, with no precautions to exclude moisture or air. The reaction mixture was then cooled to room temperature, diluted with Et_2O (5 mL) and washed with 10% aqueous Na_2CO_3 (2×5 mL). The organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure giving a brown residue, which was purified by chromatography on silica gel (3:1 to 1:1 *n*-hexane:acetone) to provide the desired spiroindolinones **4**.

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