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Enantioselective Pictet-Spengler Reactions of Isatins for the Synthesis of Spiroindolones

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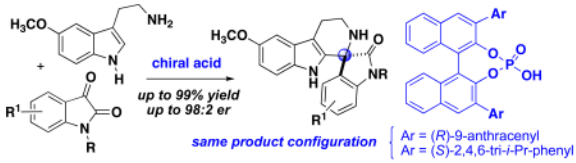
Abstract



The condensation cyclization between isatins and 5-methoxy tryptamine catalyzed by chiral phosphoric acids provides spirooxindole tetrahydro-β-carboline products in excellent yields (up to 99%) and enantioselectivity (up to 98:2 er). A comparison of catalysts provides insight for the substrate scope and factors responsible for efficient catalytic activity and selectivity in the spirocyclization. Chiral phosphoric acids with different 3,3′-substitution on the binaphthyl system and opposite axial chirality afford the spiroindolone product with the same absolute configuration.

Keywords

Isatin; Pictet-Spengler; Chiral BrØnsted Acid Catalysis; Spirooxindole

Spirocyclic oxindoles are attractive targets for synthetic organic research due to their biological activity and occurrence as the core structure in natural products.[1] This multicyclic scaffold is frequently utilized in medicinal chemistry where the chiral center and the spirocyclic fused core of these structures complements the flat heterocyclic compounds typically encountered in drug discovery programs. Thus, the use of catalytic asymmetric methods for the efficient synthesis of enantioenriched spirocycles provides an important synthetic challenge. Recent advances have provided efficient synthetic routes to access spirocyclic oxindoles containing both 5- and 6-membered ring-fused spirocyclic oxindoles.[2] Several classes of spirooxindoles have been shown to exhibit stereospecific biological activity, e.g. **MI-63**, an MDM2 inhibitor,[3] and **NITD609**, which has recently been identified as a potential treatment for Malaria based on in-vivo activity, having single dose efficacy in

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Supporting Information **Available**: Spectral data for all new compounds and X-ray crystal structure for **4aa** and **4ha**. This material is available free of charge via the Internet at www.elsevier.com.

a rodent malaria model (Figure 1).[4] Current methods often utilize expensive chiral column separations to obtain single enantiomer compounds, so asymmetric catalytic methods can provide an attractive alternative.

Here we report a chiral phosphoric acid-catalyzed enantioselective synthesis of functionalized spirooxindole tetrahydro-β-carbolines (spiroindolones) upon addition of tryptamines to isatins in a Pictet-Spengler type reaction.[5] Several examples of enantioselective Pictet-Spengler reactions have been previously reported,[6,7] but there is only one other example with isatins, recently reported while this research was in progress.[8] This study provides a comparison for several catalyst systems to determine the factors responsible for efficient catalytic activity and selectivity in this reaction, and we have observed that the 3,3′-substitution on the binaphthyl chiral catalyst directs the enantioinduction for the spirocyclization.

We initiated our investigations for the synthesis of spiroindolones by screening various catalysts for activation of chelating isatin **2a** for spirocyclization with tryptamine **3a** (Table 1). Initial screening was performed at 20 mol % of acid catalyst in the presence of Na_2SO_4. Previously in our group, chiral scandium(III) complexes have been shown to catalyze the nucleophilic addition of heteroaromatics to isatins.[9] Here we found that scandium(III) chloride exhibits high catalytic activity, affording spirocycle **4aa** in 99% yield (entry 1); however, when chiral complexes were investigated, only racemic products were obtained (entries 2-3). Using tin(II) chloride bisoxazoline complex also showed catalytic activity, but no enantioselectivity (entry 4). Because the Pictet-Spengler reaction is known to proceed through an iminium ion intermediate that is capable of forming an iminium-phosphate ion pair, we next investigated BrØnsted acids such as phosphinic acid (**7**) and chiral BINOL-derived phosphoric acid (*S*)-**8a**. These catalysts also promoted spirocycle formation in excellent yield, and (*S*)-**8a** afforded a small enantioenrichment for product **4aa** (entries 5-6). This initial screening process demonstrates that various Lewis acid and BrØnsted acid catalysts readily promote the spirocyclization with isatins.

We proceeded to compare a series of optically-pure BINOL-derived phosphoric acid catalysts and conditions to optimize the enantioselectivity.[10] Overall, high yields were observed with all phosphoric acid catalysts (**8a-e**), but anthracenyl catalyst (*R*)-**8b** in DCM was identified as the optimal catalyst, giving the highest enantioselectivity for the model reaction with 5-bromo-*N*-methylisatin (entry 7). In the process of optimization, the effect of solvent and temperature were examined for the phosphoric acid catalyzed reactions in order to improve the enantioselectivity. A variety of solvents were investigated and the choice of solvent proved to be important for the rate and enantioselectivity (entries 7-21). The use of DCM afforded high 98:2 enantioselectivity with catalyst (*R*)-**8b** while reduced enantioselectivity was observed with other solvents tested. With catalysts (*S*)-**8c** and (*S*)-**8d**, the use of several different solvents (e.g. DCM, toluene, and DMF) provided consistent, albeit moderate, enantioselectivity. Investigating lower reaction temperatures with (*S*)-**8d** did not improve the enantioselectivity (entry 18). The structure and absolute configuration of spiroindolone **4aa** was confirmed to be the (*S*)-enantiomer by X-ray crystallographic analysis.[11] It is particularly notable that the same (*S*)-enantiomer of spiroindolone was obtained for catalysts (*R*)-**8b-c** and (*S*)-**8d-e**, despite having opposite configurations of axial chirality.[12] Thus, the substituents on the binaphthyl system (e.g. anthracenyl vs. 2,4,6-tri-*i*-Pr-phenyl) direct the stereoinduction for the spirocyclization. Several instances have been reported previously where the 3,3′-substitution on the chiral phosphoric acid catalyst has been shown to reverse the sense of enantioselection.[10,13]

Based on results reported for previous thiourea-catalyzed enantioselective Pictet-Spengler reactions with aldehydes,[6] the catalytic activity and enantioselectivity for two thiourea

catalysts (**9**) were also investigated for isatins. Although high catalytic activity was observed with thiourea **9a**, only modest enantioselectivity for the (*R*)-spiroindolone was obtained in both DCM and toluene (entries 22, 23). Thiourea **9b** showed no catalytic activity in this reaction (entry 24), which indicates that the amide group of the thiourea catalyst must play an important role for the mechanism of this reaction. We also investigated the potential for dual catalysis using Lewis acid enhanced BrØnsted acidity in order to enhance the reaction rate,[14] but this led to a significant decrease in the enantioselectivity compared to the use of only phosphoric acid (*R*)-**8b** (entry 25).

Using the optimized conditions with catalyst (*R*)-**8b**, the scope of the isatin electrophile was examined with 5-methoxy tryptamine **3a** (Table 2). We also investigated the (*S*)-TRIP catalyst **8d**, previously reported by Bencivenni and coworkers,[8] as a second method for comparison between catalysts (*S*)-**8d** and (*R*)-**8b** to understand the effect of catalyst with respect to substrate scope and the observed enantioinversion. A variety of *N*-alkylated and NH isatins are successful in this reaction with moderate to high enantioselectivity for both catalyst systems. Based on the optimization of conditions with the 5-bromo-*N*-methylisatin, method A conditions with catalyst (*R*)-**8b** give improved enantioselectivity for halide-substituted isatins relative to catalyst (*S*)-**8d**. The DMF conditions of method B are particularly well-suited for NH isatins, which we attribute to solubility. Generally, the formation of the imine intermediate was rarely observed and not isolated for this reaction. One exception is based on investigations of the *N*-acetyl isatin, which afforded only the imine product with trace amount of spirocyclization (entry 10). The *N*-propargyl spiroindolone can also be accessed in good yield and enantioselectivity (entry 8), providing an alkyne functional handle for further diversification.

The scope of the tryptamine was also examined for spirocyclization, providing insight into the limitations of this methodology (Table 3). While the 5-methoxy tryptamine (Table 2) and unsubstituted tryptamine both proceed with high yield and moderate to high enantioselectivity, the enantioselectivity of the spirocyclization deteriorates with other substitution patterns. The position of the methoxy group on tryptamine also effects the level of enantioslectivity, where the 6-methoxytryptamine proceeds with poor enantioselectivity (60:40 er) relative to the 5-methoxy tryptamine (92:8 er) (Table 3 entries 1-2 vs Table 2, entry 2). Although the addition of unsubstituted tryptamines to isatin have been previously investigated by Bencivenni and coworkers,[8] we found that halide substitution at the 5-position of *N*-methyl isatin leads to an errosion of selectivity in comparison with the unsubstitiuted methyl isatin (entries 3-6). The geminally-disubstituted tryptamine **3d** was also investigated because this substrate has been utilized previously to promote cyclization with aldehydes by exploiting the Thorpe-Ingold effect.[7a] While tryptamine **3d** was surprisingly unreactive with catalyst (*R*)-**8b** and (*S*)-**8d**, using catalyst (*S*)-**8e** afforded high yields of product, albeit with minimal enantioselectivity (entries 7-9). This result indicates that the steric effects of the geminal disubstitution may inhibit formation of the iminium-phosphate ion complex necessary to induce asymmetry, although product formation is still observed with a more acidic catalyst.[15]

The proposed mechanism for the spiroindolone synthesis is initiated by formation of an iminium-phosphate ion complex with the chiral phosphoric acid catalyst (Scheme 1).[5] Intramolecular attack of the nucleophilic indole from the 2-position leads to spirocyclization and formation of the new chiral carbon center. The resulting indolenium ion undergoes an elimination to restore aromaticity, generating spiroindolone **4** and regenerating the catalyst. We have noted that using different 3,3′-substitution on the binaphthyl system with the opposite axial chiral configuration (e.g. (*S*)-**8d** and (*R*)-**8b**) affords the spiroindolone with the same absolute configuration. Therefore, the same axial configuration of catalyst can afford an inversion in the sense of enantioselection for the spirocyclization. This inversion is

attributed to the steric interactions that exist upon formation of the iminium-phosphate ion complex with the 9-anthracenyl catalyst (*R*)-**8b**, thereby reversing the approach of the indole to the iminium ion.

In conclusion, we have developed a catalytic asymmetric method for accessing a variety of functionalized spiroindolones from isatins, including halide substitution patterns found in the anti-malaria lead compound **NITD609**. A comparison of the 9-anthracenyl catalyst (*R*)-**8b** and the (*S*)-TRIP catalyst (**8d**) provides insight into the substrate scope as well as the effect of different solvent and catalyst combinations that are needed in order to obtain optimal yields and enantioselectivities. The (*S*)-spiroindolone product is obtained for both the (*S*)-TRIP and (*R*)-anthracenyl catalysts, which indicates that the substitution on the binaphthyl system directs the sense of enantioselection. Transition state studies to investigate this observed inversion are currently in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. This X-ray structure confirms the absolute configuration that was previously determined as the (S)-enantiomer by simulation of the electronic circular (ECD) dichroism spectra, see reference 8.
12. The absolute configurations for chiral phosphoric acids in this study are based on products purchased from Sigma-Aldrich. (*R*)-3,3′-Bis(9-anthracenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate is product #695718 and lot# MKBG2357V was used for these studies with an optical rotation of +139.3 (c = 1%, chloroform), as provided by Sigma-Aldrich. Akiyama and co-workers report $[\alpha]_D^{26}$ −24.9 (c 1.00, EtOH), for the (*R*)-anthracenyl acid, see: Akiyama T, Morita H, Fuchibe K. J Am Chem Soc. 2006; 128:13070–13071. [PubMed: 17017784]
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15. We have also investigated reactions of racemic α- and β-substituted tryptamines to determine if a chiral resolution and stereospecific cyclization would occur. In both cases, moderate yield is observed, and only racemic products were obtained resulting from the diastereoselective nature of the reaction.

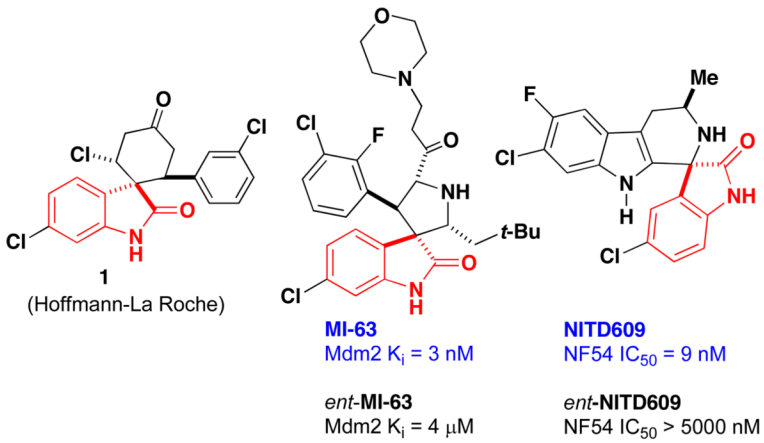


Figure 1. Examples of Biologically Active Spirooxindoles

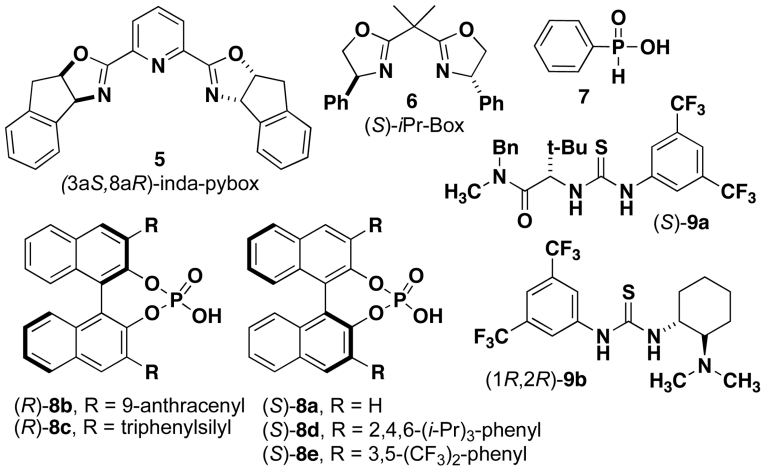
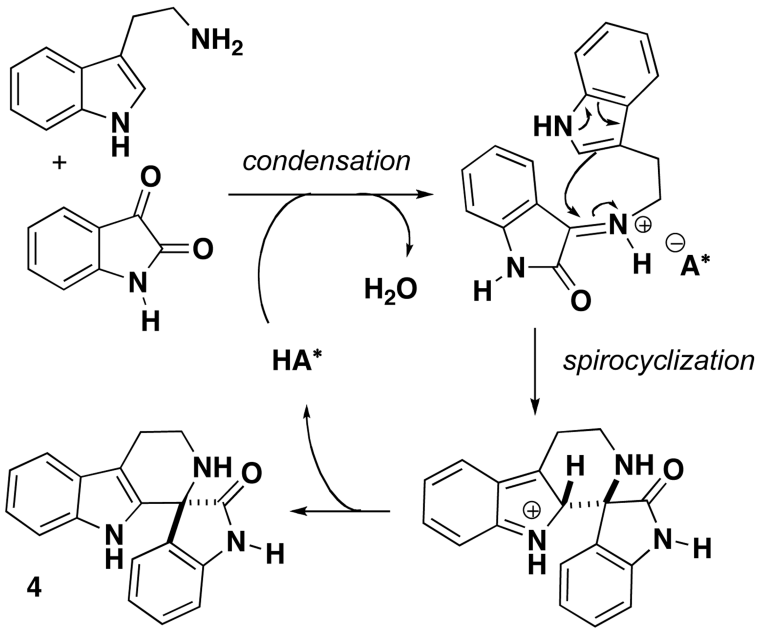
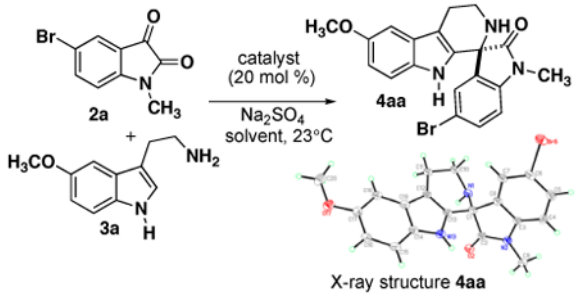


Figure 2. Structures of Chiral Ligands and Catalysts Investigated



Scheme 1. Catalytic Cycle for Spirocyclization

Table 1
Catalyst Optimization for Spiroindolone Formation



entry	catalyst	solvent	yield (%)[a]	er (config)[b]
1	$ScCl_3$	CH_2Cl_2	99	--
2	$ScCl_3$•**5**	CH_2Cl_2	83	52:47 (*R*)
3	$ScCl_2(SbF_6)$•**5**	CH_2Cl_2	99	54:46 (*R*)
4	$SnCl_2$•**6**	CH_2Cl_2	86	51:49 (*R*)
5	**7**	CH_2Cl_2	99	--
6	(*S*)-**8a**	CH_2Cl_2	99	58:42 (*R*)
7	(*R*)-**8b**	CH_2Cl_2	99	92:8 (*S*)
8	(*R*)-**8b**	CH_3Ph	91	80:20 (*S*)
9	(*R*)-**8b**	CH_2Cl_2/DMF[d]	99	56:44 (*S*)
10	(*R*)-**8b**	DMF	45	65:45 (*S*)
11	(*R*)-**8b**	EtOAc	76	60:40 (*S*)
12	(*R*)-**8c**	CH_2Cl_2	76	76:24 (*S*)
13	(*R*)-**8c**	CH_3CN	86	85:15 (*S*)
14	(*R*)-**8c**	THF	80	80:20 (*S*)
15	(*R*)-**8c**	$CHCl_3$	77	60:40 (*S*)
16	(*S*)-**8d**	CH_2Cl_2	nd	73:23 (*S*)
17	(*S*)-**8d**	CH_3Ph	92	82:18 (*S*)
18	(*S*)-**8d**	CH_3Ph[e]	90	83:17 (*S*)
19	(*S*)-**8d**	CH_2Cl_2/DMF[c]	90	80:20 (*S*)
20	(*S*)-**8d**	DMF	70[d]	82:18 (*S*)
21	(*S*)-**8e**	CH_2Cl_2	99	68:32 (*S*)
22	**9a**	CH_2Cl_2	99	75:25 (*R*)
23	**9a**	CH_3Ph	60	76:24 (*R*)
24	**9b**	CH_2Cl_2	NR	--
25	(*R*)-**8b**/MgF_2	CH_3Ph	85	77:23 (*S*)

Reactions performed with 1.2 equiv of isatin under argon. Reactions run from 48-96h.

[a]Isolated yield.

[b] Enantioselectivity determined by HPLC analysis using chiral stationary phase.

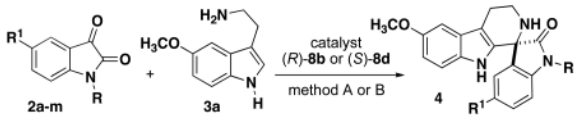
[c] 4:1 DCM/DMF.

[d] 40°C.

[e] Reaction performed at -15°C.

Table 2

Scope of Isatins for Phosphoric acid-catalyzed Spirocyclization



entry	R	R^1	product	method	yield (%)[a]	er[b]
1	CH_3	Br	**4aa**	A	99	91:9
				B	70	82:18
2	CH_3	Cl	**4ba**	A	99	92:8
				B	90	88:12
3	CH_3	H	**4ca**	A	99	88:12
				B	99	95:5
4	CH_3	OCH_3	**4da**	A	99	58:42
				B	79	70:30
5	Bn	H	**4ea**	A	99	82:18
				B	95	97:3
6	PMB	H	**4fa**	A	72	87:13
				B	87	93:7
7	PMB	Br	**4ga**	A	86	87:13
				B	81	75:25
8	CH_2CCH	F	**4ha**	A	60	92:8
				B	86	92:8
9	Ph	H	**4ia**	A	99	85:15
				B	44	97:3
10	Ac	H	**4ja**	A	87[c]	--
				B	53[c]	--
11	H	H	**4ka**	A	66	94:6
				B	99	94:6
12	H	Cl	**4la**	A	99	84:16
				B	88	80:20

entry	R	R^1	product	method	yield (%)[a]	er[b]
13	H	OCH_3	**4ma**	A	84	97:3
				B	92	96:4

Method A: 20 mol % catalyst (*R*)-**8b** in CH_2Cl_2 at 23°C for 72-96h.

Method B: 10 mol % catalyst (*S*)-**8d** in DMF at 40°C for 24-48h.

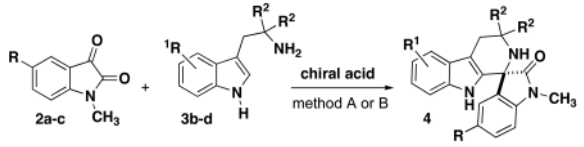
[a] Isolated yield.

[b] Enantioselectivity determined by chiral phase HPLC.

[c] Yield is for imine.

Table 3

Tryptamine Investigation for Phosphoric Acid-catalyzed Spirocyclization



entry	product	R	R^1	R^2	method	chiral acid	yield %[a]	er[b]
1	**4bb**	Cl	6-OCH_3	H	A	**8b**	99	60:40
2	**4bb**	Cl	6-OCH_3	H	B	**8d**	39	80:20
3	**4bc**	Cl	H	H	A	**8b**	93	67:33
4	**4bc**	Cl	H	H	B	**8d**	89	65:35
5	**4cb**	H	H	H	A	**8b**	35	95:5
6	**4cb**	H	H	H	B	**8d**	71	95:5
7	**4bd**	Cl	H	CO_2CH_3	A	**8b**	no rxn	--
8	**4ad**	Br	H	CO_2CH_3	B	**8d**	21	52:48
9	**4ad**	Br	H	CO_2CH_3	A	**8e**	92	59:41

Method A: 20 mol % catalyst in CH_2Cl_2 at 23°C for 72-96h.

Method B: 10 mol % catalyst in DMF at 40°C for 24-48h.

[a] Isolated yield.

[b] Enantioselectivity determined by chiral phase HPLC.