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Construction of Chiral Tetrahydro-β-Carbolines through Asymmetric Pictet-Spengler Reaction of Indolyl Dihydropyridines

Shou-Guo Wang[†§], Zi-Lei Xia[†§], Ren-Qi Xu[†], Xi-Jia Liu[†], Chao Zheng[†], and Shu-Li You[†‡*]

Abstract: A highly efficient synthesis of enantioenriched tetrahydro-β-carbolines is developed *via* chiral phosphoric acid-catalyzed Pictet-Spengler reaction of indolyl dihydropyridines. The reaction proceeds under mild conditions to afford the desired chiral tetrahydro-β-carbolines in good to excellent yields (up to 96%) and high enantioselectivity (up to 99% *ee*). With this method, a formal synthesis of Tangutorine and a total synthesis of Deplancheine were achieved in a highly efficient manner.

The chiral tetrahydro-β-carboline ring systems are attractive synthetic targets as they are structural cores of many indole alkaloids and pharmaceuticals, such as Deplancheine, Tangutorine, Geissoschizine, and Vallesiachotamine (Figure 1).[1] The appealing architecture and significant biological activities of these tetrahydro-β-carboline alkaloids have received considerable attention among the synthetic and medicinal chemists.[2] The catalytic asymmetric Pictet-Spengler reactions has been emerged as one of the most efficient and straightforward methods, providing direct access to the enantioenriched tetrahydro-β-carbolines.[3] Pioneering studies by Jacobsen, List, Hiemstra and many others have been carried out on highly enantioselective Pictet-Spengler type reactions.[4] However, to date, most of the reported Pictet-Spengler reactions focused on the combination of tryptamine derivatives and carbonyl functionality under acidic conditions. The development of novel efficient catalytic reactions from alternative readily available substrates for the construction of enantioenriched tetrahydro-β-carbolines is highly desirable.

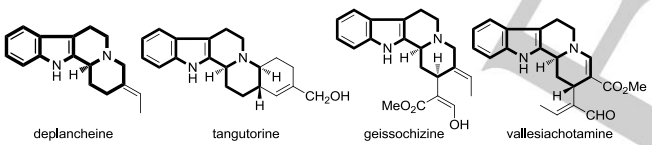
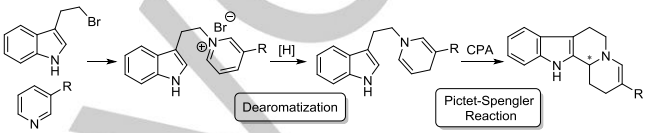


Figure 1. Selected natural products containing a tetrahydro-β-carboline motif.

Meanwhile, asymmetric dearomatization reaction of pyridines represents an intriguing protocol to afford chiral piperidines and related alkaloids.[5] Recently, we reported a chiral phosphoric acid catalyzed hydrogenative dearomatization/*aza*-Friedel-Crafts sequence of substituted pyridines, affording the enantioenriched piperidines.[6] As part of our ongoing research on dearomatization reactions, we envisioned that a reductive dearomatization/Pictet-Spengler reaction sequence from simple indole and pyridine substrates could afford the enantioenriched tetrahydro-β-carbolines (Scheme 1). Herein, we report such a facile and efficient synthesis of chiral piperidine fused tetrahydro-β-carbolines *via* chiral phosphoric acid (CPA) catalyzed Pictet-Spengler reaction of indolyl dihydropyridines.



Scheme 1. Dearomatization/Pictet-Spengler reaction sequence. R = electron withdrawing group, CPA = chiral phosphoric acid.

We began our studies by investigating different chiral phosphoric acids in the Pictet-Spengler reaction of 1,4-dihydropyridine **2a**, readily prepared from 3-(2-bromoethyl)-1*H*-indole and 3-acetylpyridine.[7] In the presence of a range of chiral phosphoric acids, all the reactions proceeded smoothly in toluene at room temperature to afford the desired tetrahydro-β-carboline **3a** in variable yields and moderate enantioselectivity (Table 1). The evaluation of chiral phosphoric acids with regard to different substituents and backbones indicated that (*R*)-SPINOL-derived catalyst **1h**[8] was an efficient catalyst, converting **2a** to the desired product **3a** with the best enantioselectivity (80% yield, 62% *ee*, entry 8, Table 1).

Encouraged by these promising results, we set out to further optimize the reaction conditions. Evaluation of solvents disclosed that carbon tetrachloride is the best option in terms of yield and enantioselectivity (85% yield, 72% *ee*, entry 14, Table 1). To our delight, 3 Å molecular sieves could improve the enantioselectivity significantly, furnishing the target tetrahydro-β-carboline **3a** in 90% yield and 91% *ee* with a prolonged reaction time (entry 15, Table 1). Lowering the reaction temperature to 0 °C led to decreased yield without notable increase of the enantioselectivity (45% yield, 92% *ee*, entry 18, Table 1). Therefore, the optimal reaction conditions for this reaction were determined as follows: 10 mol% chiral phosphoric acid **1h**, 3 Å molecular sieves as the additive in CCl_4 at room temperature. The absolute configuration of the product was determined by comparison of the specific rotation of product **3a** to literature data.[9]

Having established the optimal reaction conditions, the substrate scope was then investigated to examine the generality of the reaction. The results are summarized in Scheme 2. The reaction conditions tolerated a wide range of electron-withdrawing substituents, such as alkyl ketone, ester and cyano group on the C3' position of the 1,4-dihydropyridine core, providing their corresponding products in good to excellent yields and excellent enantioselectivity (**3a** to **3g**, 67-95% yields, 88-96% *ee*, Scheme 2). To be noted, substrate **2c** containing a

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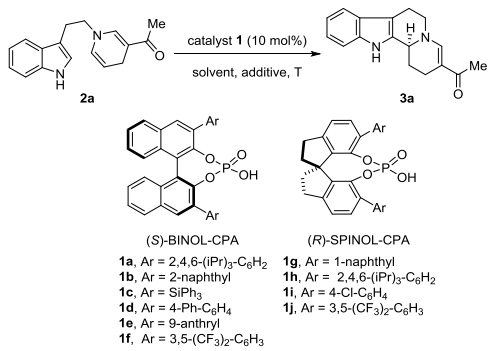
cyclohex-2-enone motif was also compatible for this reaction, affording the desired product **3c** in 75% yield and 90% *ee*.

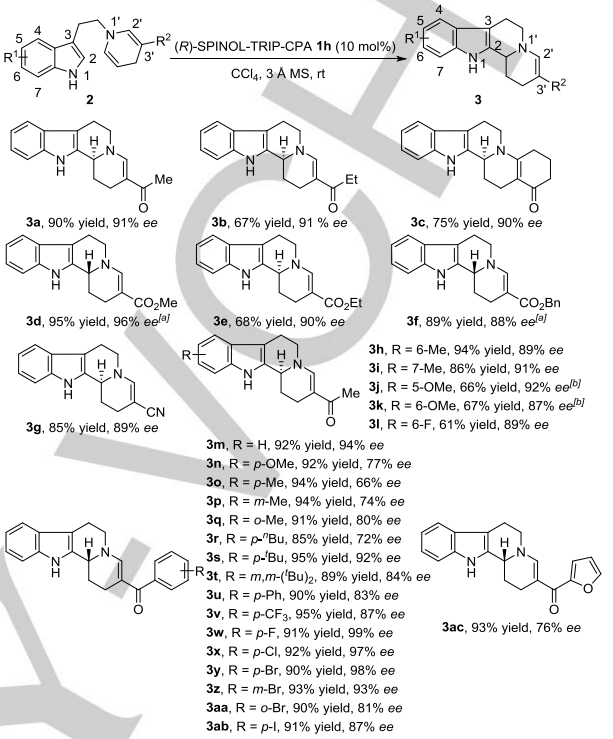
Table 1: Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Additive	t/h	Yield (%)[b]	*ee* (%)[c]
1	**1a**	toluene	--	3.5	66	38
2	**1b**	toluene	--	10	42	10
3	**1c**	toluene	--	3.5	56	31
4	**1d**	toluene	--	3.5	10	14
5	**1e**	toluene	--	3.5	81	25
6	**1f**	toluene	--	3.5	80	11
7	**1g**	toluene	--	3.5	70	35
8	**1h**	toluene	--	3.5	80	62
9	**1i**	toluene	--	3.5	69	20
10	**1j**	toluene	--	3.5	81	40
11	**1h**	benzene	--	3.5	77	62
12	**1h**	DCM	--	3.5	83	55
13	**1h**	$CHCl_3$	--	3.5	95	47
14	**1h**	CCl_4	--	3.5	85	72
15	**1h**	CCl_4	3 Å MS	12	90	91
16	**1h**	CCl_4	4 Å MS	12	90	89
17	**1h**	CCl_4	5 Å MS	8	82	74
18[d]	**1h**	CCl_4	3 Å MS	36	45	92

[a] Reactions were performed with **2a** (0.1 mmol), **1** (10 mol%) and additive in 2.0 mL solvent at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] At 0 °C.

The effect of substituent on the indole core was then examined. Either an electron-donating group (6-Me, 7-Me, 5-OMe, 6-OMe) or an electron-withdrawing group (6-F) on the indole ring was well tolerated. The corresponding products were obtained in moderate to excellent yields and high enantioselectivity (**3h** to **3l**, 61-94% yields, 87-92% *ee*, Scheme 2). For the more reactive substrates **2j** and **2k**, the reactions were carried out at 0 °C. The desired products could be obtained in reasonable yields and excellent enantioselectivity (**3j**, 66% yield, 92% *ee*; **3k**, 67% yield, 87% *ee*). Substrate **2l** bearing 6-F substituent was well tolerated, affording product **3l** in 61% yield and 89% *ee*.

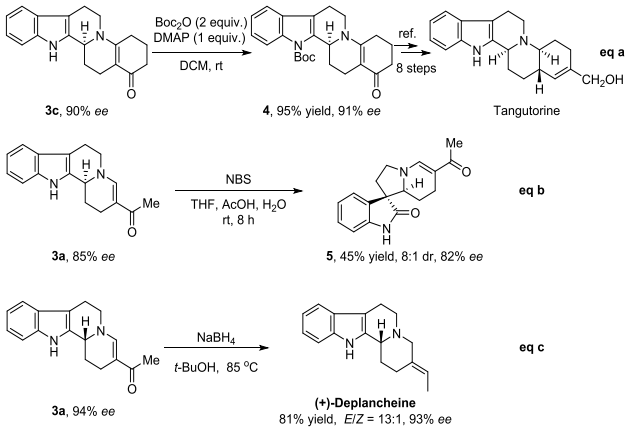


Scheme 2. Substrate scope. [a] For **3d**, **3f** and **3m**-**3ac**, (*S*)-**1h** was used. [b] At 0 °C.

To further explore the substrate scope, substrates bearing an aryl ketone at the 3' position of the 1,4-dihydropyridine core were further explored. As shown in Scheme 2, the reaction of substrate **2m** afforded the corresponding product **3m** in 92% yield and 94% *ee*. Various substrates containing electron-donating group substituted aryl ketone [*p*-OMe, *p*-Me, *m*-Me, *o*-Me, *p*-^{n}Bu, *p*-^{t}Bu, *m*,*m*-(^{t}Bu)$_2$] underwent the Pictet-Spengler reaction smoothly affording products **3n**-**3t** in excellent yields and good to excellent enantioselectivity (85-95% yield, 66-92% *ee*). Notably, the introduction of *para*-phenyl group (**2u**) was also tolerated to give **3u** in 90% yield and 83% *ee*. Interestingly, electron-withdrawing group and halogen substituent (*p*-CF_3, *p*-F, *p*-Cl, *p*-Br, *m*-Br, *o*-Br, *p*-I) were well compatible for the asymmetric Pictet-Spengler reaction (90-95% yields, 81-99% *ee*). Particularly, the installation of F, Cl, Br at the *para* position could significantly increase the enantioselective control, although the mechanism is still unclear. Finally, furyl ketone (**2ac**) was also tolerated, and **3ac** was obtained in 93% yield and 76% *ee*.

To highlight the utility of this enantioselective Pictet-Spengler reaction, transformations of products were conducted. As shown in Scheme 3, treatment of product **3c** with Boc_2O in the presence of DMAP gave the Boc protected indole **4** in 95% yield and 91% *ee* (eq a), which was known as the key intermediate for the total synthesis of Tangutorine.[10] The oxidative rearrangement of tetrahydro-β-carboline **3a** utilizing *N*-bromosuccinimide as the oxidant led to tetracyclic 3-spirooxindole **5** in good

stereochemical integrity and high diastereoselectivity (45% yield, 8:1 d.r., 82% *ee*, eq b).[11] The spirooxindole is an intriguing structural motif in many alkaloids, natural products and pharmaceuticals.[12] Finally, the reduction of product **3a** was successfully carried out with $NaBH_4$ as the reductive reagent,[9] affording (+)-Deplancheine with high *E*/*Z* selectivity and excellent enantioselectivity (81% yield, *E*/*Z* = 13:1, 93% *ee*, eq c).



Scheme 3. Transformations of the products.

In summary, we have developed a highly efficient synthesis of enantioenriched tetrahydro-β-carbolines *via* chiral phosphoric acid-catalyzed Pictet-Spengler reaction of indolyl dihydropyridines. Different from previous enantioselective Pictet-Spengler reactions utilizing tryptamines and carbonyl compounds as substrates, the current protocol employs substrates readily prepared from simple indoles and pyridines. Under mild conditions, these reactions proceeded smoothly affording chiral tetrahydro-β-carbolines in good to excellent yields (up to 96%) and high enantioselectivity (up to 99% *ee*). A concise formal synthesis of Tangutorine and total synthesis of Deplancheine further demonstrated the synthetic utility of this newly developed methodology.

Acknowledgements

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Keywords: asymmetric catalysis • chiral phosphoric acid • dearomatization • organocatalysis • Pictet-Spengler • tetrahydro-β-carboline

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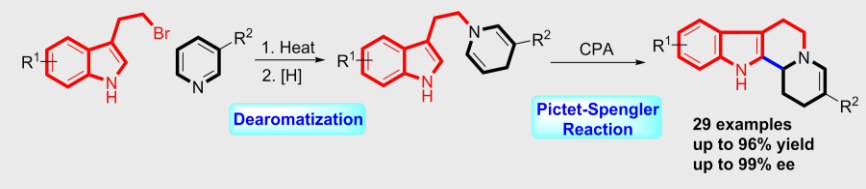

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