Asymmetric Catalysis

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Hydrogenative Dearomatization of Pyridine and an Asymmetric Aza-Friedel–Crafts Alkylation Sequence**

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Abstract: *Highly efficient synthesis of enantiomerically enriched substituted piperidines has been realized via chiral phosphoric acid catalyzed cascade hydrogenative dearomatization of substituted pyridines and aza-Friedel-Crafts reaction in good to excellent yields and enantioselectivity.*

Piperidine represents an intriguing scaffold widely distributed in natural products having significant biological activities, and therapeutic agents[1] (Figure 1). Therefore, tremendous effort has been devoted to the development of efficient methods for the synthesis of this privileged structure.[2] Despite extensive efforts, catalytic asymmetric synthesis of substituted piperidines by direct functionalization of pyridine remains scarce. In this regard, catalytic asymmetric nucleophilic additions to the pyridinium salts[3] and reduction of substituted pyridines[4] are frequently utilized strategies. Asymmetric additions to the pyridinium salts are limited to the nucleophiles such as cyanide,[3a] alkynes,[3b,c] dialkylzinc,[3d] and boronic acid.[3e] For direct asymmetric reduction of the pyridine core, precious metals such as iridium, rhodium, ruthenium, and palladium are in general required to assure the efficiency.[4c–i] Meanwhile, organocatalytic enantioselective transfer hydrogenation of pyridines using a Hantzsch ester as a hydrogen source has witnessed significant progress.[5] With our continuing interest in asymmetric dearomatization reactions,[6] we envisaged that a hydrogenative dearomatization of pyridine/asymmetric aza-Friedel–Crafts sequence (pyrrole as the nucleophile[7]) could provide efficient access to a chiral piperidine scaffold (Scheme 1). It is noteworthy that the pyrrole core is also a prominent feature in numerous biologically interesting natural products and pharmaceuticals. Therefore, the synthesis of compounds with such embedded motifs is highly desirable.[8]

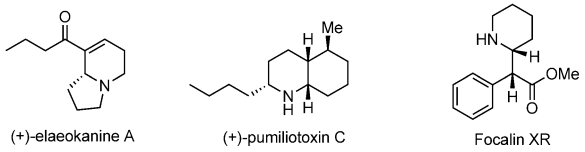
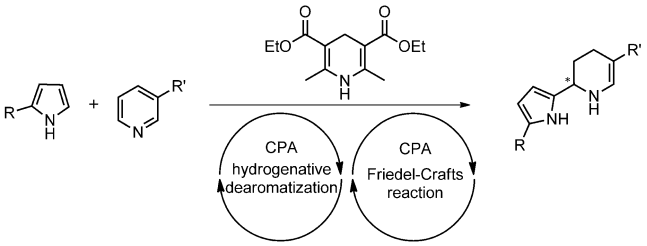


Figure 1. Selected natural products and a drug containing a piperidine motif.



Scheme 1. The design of a CPA-catalyzed cascade reaction. CPA = chiral phosphoric acid.

We began our study by choosing 2-phenylpyrrole (**3a**) and 3-benzoylpyridine (**4a**) as the model substrates, and subjected them to the Hantzsch ester **2** with a chiral phosphoric acid as the catalyst (Table 1). In the presence of 10 mol% (*S*)-binol-TRIP (**1a**) in dichloromethane at room temperature, the reaction proceeded smoothly to afford the desired product **5a** in 64% yield and 57% *ee* within 24 hours (entry 1, Table 1). To increase the enantioselectivity of this cascade reaction, various chiral phosphoric acids were tested. To our great delight, when (*R*)-spinol-TRIP (**1j**)[9] was employed as the catalyst, the reaction gave the best enantioselectivity (entry 10, Table 1).

Further screening of solvents (entries 1–7, Table 2) revealed that dichloromethane remained the optimal solvent in terms of enantioselectivity. Interestingly, molecular sieves significantly accelerated the reaction rate to afford a high conversion. With 4 Å molecular sieves as an additive and a prolonged reaction time, the yield increased to 94% without affecting the enantioselectivity of the reaction (entry 12, Table 2). Further efforts were made to improve the enantioselectivity by lowering the reaction temperature to 0°C, however, the reaction was sluggish under these conditions. Only 20% yield of **5a**, albeit with an improved enantioselectivity (92% *ee*), could be obtained even with a prolonged reaction time (entry 14, Table 2).

Under the optimal reaction conditions, the substrate scope was explored to test the generality of the reaction. The results are summarized in Table 3. The cascade reaction

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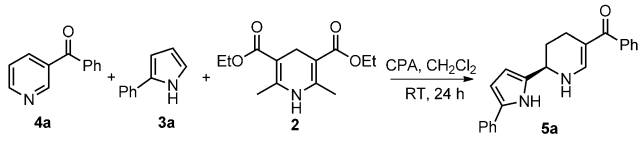
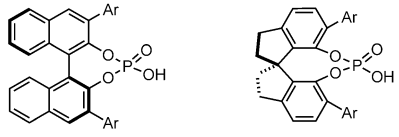
Table 1: Screening of chiral phosphoric acid catalysts.





(*S*)-binol CPA

(*R*)-spinol CPA

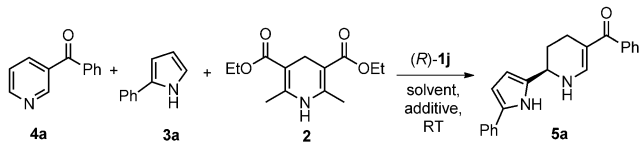
1a, Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$
1b, Ar = 2-naphthyl
1c, Ar = SiPh$_3$
1d, Ar = 4-*t*Bu-2,6-*i*Pr$_2$C$_6$H$_2$
1e, Ar = 4-PhC$_6$H$_4$
1f, Ar = 9-anthryl

1g, Ar = 1-naphthyl
1h, Ar = 2,5-(CF$_3$)$_2$C$_6$H$_3$
1i, Ar = 4-ClC$_6$H$_4$
1j, Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$

Entry[a]	**1**	Yield [%][b]	*ee* [%][c]
1	**1a**	64	57
2	**1b**	75	13
3	**1c**	85	30
4	**1d**	74	60
5	**1e**	73	4
6	**1f**	85	29
7	**1g**	84	6
8	**1h**	47	23
9	**1i**	90	26
10	**1j**	33	88

[a] Reactions were performed with 3-benzoylpyridine (0.2 mmol), Hantzsch ester **2** (0.24 mmol), 2-phenylpyrrole (0.24 mmol), **1** (10 mol%) in 2 mL CH_2Cl_2. [b] Yield of isolated produt. [c] Determined by HPLC.

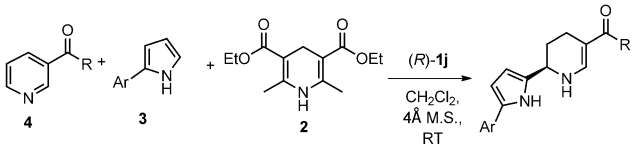
Table 2: Screening of solvents, additives, and reaction temperature.



Entry[a]	Solvent/additive	*t* [h]	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	24	33	88
2	toluene	24	63	77
3	$ClCH_2CH_2Cl$	24	45	69
4	CH_3CN	24	15	57
5	$CHCl_3$	24	42	67
6	THF	24	10	69
7	PhCl	24	53	81
8	CH_2Cl_2/3 Å M.S.	24	52	89
9	CH_2Cl_2/4 Å M.S.	24	81	89
10	CH_2Cl_2/5 Å M.S.	24	52	89
11	CH_2Cl_2/$MgSO_4$	24	36	88
12	CH_2Cl_2/4 Å M.S.	36	94	88
13	CH_2Cl_2/4 Å M.S.	48	95	88
14[d]	CH_2Cl_2/4 Å M.S.	84	20	92

[a] Reactions were performed with 3-benzoylpyridine (0.2 mmol), Hantzsch ester **2** (0.24 mmol), 2-phenylpyrrole (0.24 mmol), **1j** (10 mol%), and additive (100 mg) in 2 mL solvent at room temperature. [b] Yield of isolated product. [c] Determined by HPLC. [d] The reaction was carried out at 0 °C. M.S. = molecular sieves, THF = tetrahydrofuran.

Table 3: Substrate scope for the cascade reaction.

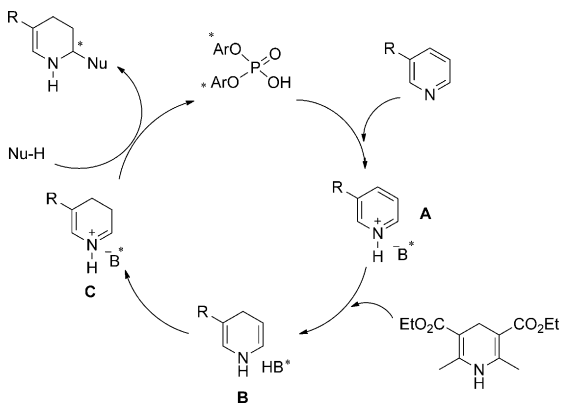


Entry[a]	Ar	R	*t* [h]	Yield [%][c]	*ee* [%][d]
1	4-FC$_6$H$_4$	Ph	60	72 (**5b**)	85
2	2-ClC$_6$H$_4$	Ph	72	70 (**5c**)	88
3	2-FC$_6$H$_4$	Ph	72	93 (**5d**)	87
4	3-MeC$_6$H$_4$	Ph	60	95 (**5e**)	87
5	4-MeOC$_6$H$_4$	Ph	60	94 (**5f**)	82
6	Ph	2-naphthyl	60	74 (**5g**)	89
7	Ph	4-*t*BuC$_6$H$_4$	48	73 (**5h**)	87
8	Ph	1-naphthyl	72	70 (**5i**)	90
9	Ph	4-FC$_6$H$_4$	72	91 (**5j**)	86
10	Ph	4-MeOC$_6$H$_4$	60	92 (**5k**)	87
11	Ph	4-BrC$_6$H$_4$	60	93 (**5l**)	90
12	Ph	4-MeC$_6$H$_4$	72	93 (**5m**)	89
13	Ph	3-NO$_2$C$_6$H$_4$	60	95 (**5n**)	89
14	Ph	2-thienyl	72	78 (**5o**)	89
15	Ph	Me	72	94 (**5p**)	96
16	Ph	Et	72	90 (**5q**)	83

[a] Reactions were performed with 3-benzoylpyridine (0.2 mmol), Hantzsch ester **2** (0.24 mmol), 2-phenylpyrrole (0.24 mmol), **1j** (10 mol%), and 4 Å M.S. (100 mg) in 2 mL CH_2Cl_2. [b] Yield of isolated product. [c] Determined by HPLC.

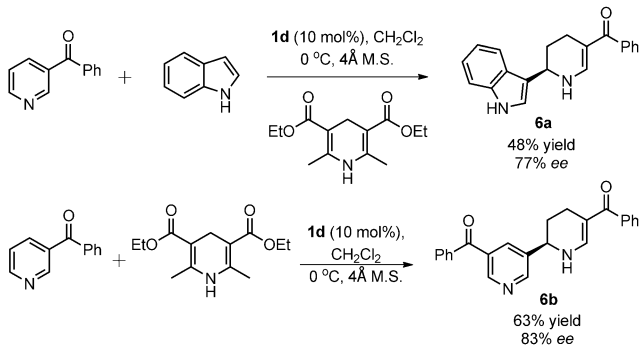
tolerated a wide range of 2-arylpyrroles bearing either an electron-donating or electron-withdrawing substituent on the aryl group. The reactions of 3-benzoylpyridine with the 2-arylpyrroles **3b–f** were tested. In all cases, good to excellent yields and enantioselectivity were achieved (**5b–f**; Table 3). In addition, the reactions of various 3-acylpyridines were also carried out. High yields and enantioselectivity were obtained for 3-acylpyridines bearing either an electron-rich aryl group (4-*t*BuC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$) or electron-poor aryl group (4-FC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$). Moreover, both naphthalen-2-yl(pyridin-3-yl)methanone and naphthalen-1-yl(pyridin-3-yl)methanone were suitable substrates for the cascade reaction (**5g** and **5i**). The substrate **4o** with a 2-thienyl group was also well tolerated, and the corresponding product was obtained in 78% yield and 89% *ee*. To our delight, the asymmetric cascade reaction of 3-acetylpyridine led to the product in 94% yield and 96% *ee* (**5p**). When 3-propionylpyridine was used, the reaction also proceeded smoothly in 90% yield and 83% *ee* (**5q**). The absolute configuration of enantiopure **5l**, recrystallized from petroleum ether and dichloromethane, was confirmed by an X-ray crystallographic analysis as *R*.[10]

Regarding the mechanism of this cascade reaction, it is proposed that the first step is protonation of the pyridine by the phosphoric acid catalyst to generate the pyridinium salt **A** (Scheme 2). Then, the reduction of **A** by 1,4-hydride transfer from the Hantzsch ester **2** generates the enamine intermediate **B**, which then isomerizes to the iminium **C** in the presence of phosphoric acid. Subsequent asymmetric aza-Friedel–Crafts reaction will generate the desired product and then release the phosphoric acid.



Scheme 2. Plausible catalytic cycle. HB* = chiral phosphoric acid.

To further extend the substrate scope for the cascade reaction with 3-benzoylpyridine, indole was used as a nucleophile under slightly modified reaction conditions (Scheme 3). With (*S*)-**1d** as the catalyst, the cascade reaction proceeded smoothly to give the product **6a** in 48% yield and



Scheme 3. CPA-catalyzed cascade reaction with indole and without a nucleophile.

77% *ee*. Interestingly, in the absence of an additional nucleophile, the product **6b**, containing a dipiperidine framework, was obtained in 63% yield and 83% *ee*. Notably, the corresponding dipiperidine framework is an important structural building block of many alkaloids, including anabasine, astrophylline, and hoveine.[11]

In summary, we have developed a highly efficient synthesis of enantiomerically enriched substituted piperidines by the chiral phosphoric acid catalyzed hydrogenative dearomatization /aza-Friedel–Crafts sequence of substituted pyridines with up to 95% yield and 96% *ee*. The newly developed methodology features readily available starting materials and mild reaction conditions. The results from the current study provide a new synthetic route for chiral piperidines and novel concepts in desigining catalytic cascade reactions. Further applications of this cascade into other transformations are currently underway in our laboratory.

Experimental Section

In a Schlenk tube, the catalyst (*R*)-**1j** (14.3 mg, 0.02 mmol), substituted pyridine **4** (0.2 mmol), Hantzsch ester **2** (60.7 mg, 0.24 mmol), 2-arylpyrrole **3** (0.24 mmol), and 4 Å M.S. (100 mg) were dissolved in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature. After the reaction was complete (as monitored by TLC), the reaction mixture was quenched with aq. $NaHCO_3$ and extracted with CH_2Cl_2. The dichloromethane layer was washed with brine, dried over Na_2SO_4, and filtrated. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (acetone/petroleum ether 1:4) to afford product **5**.

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