

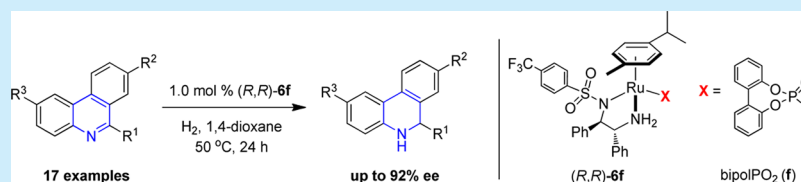
# Ruthenium-Catalyzed Enantioselective Hydrogenation of Phenanthridine Derivatives

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**S** Supporting Information



**ABSTRACT:** The first asymmetric hydrogenation of phenanthridines catalyzed by chiral cationic ruthenium diamine complexes has been developed with up to 92% ee and full conversions. The choice of the counteranion of the catalyst was found to be critical for achieving high enantioselectivity. In addition, the obtained 5,6-dihydrophenanthridine could be used as a chiral hydride donor for organocatalytic asymmetric transfer hydrogenation.

The 5,6-dihydrophenanthridines are important structural units in natural products and biologically active molecules,<sup>1</sup> such as those outlined in Figure 1. To date, a

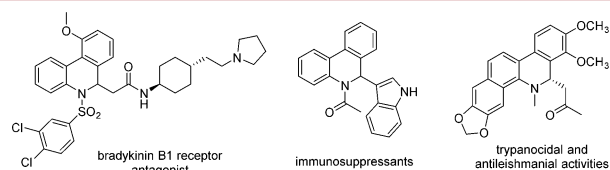


Figure 1. Selected biologically active compounds.

number of methods have been developed for the preparation of 6-substituted 5,6-dihydrophenanthridine derivatives.<sup>2</sup> In addition, recent research has shown that the chirality of 6-substituted 5,6-dihydrophenanthridines plays a very important role in determining their bioactivity.<sup>1c</sup> However, few catalytic asymmetric approaches for obtaining such chiral compounds were reported.<sup>1e,3</sup> Most recently, Lautens reported the enantioselective synthesis of a wide range of 6-aryl-substituted 5,6-dihydrophenanthridine derivatives through retro-carbopalladation of chiral *o*-bromobenzylamines with excellent ee values.<sup>3a</sup>

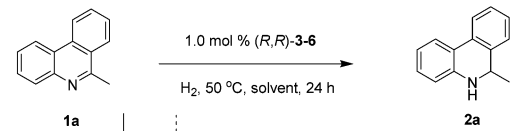
In the past decade, asymmetric hydrogenation of heteroaromatic compounds has become one of the most straightforward paths toward the synthesis of optically active compounds with chiral heterocyclic skeletons.<sup>4</sup> For example, since the pioneering work on asymmetric hydrogenation of quinolines reported by Zhou,<sup>5a</sup> numerous iridium complexes containing chiral phosphorus ligands have proven to be effective in the asymmetric hydrogenation of quinolines and isoquinolines.<sup>5</sup>

However, to the best of our knowledge, the asymmetric hydrogenation of phenanthridines has not been documented yet.<sup>6</sup> This is probably due to the following two facts: (1) the asymmetric hydrogenation of heteroarenes consisting of more than two fused aromatic rings is still difficult because of the possibility of dehydronative aromatization of the reduced products,<sup>6b,7</sup> and (2) the strong coordinative nitrogen atom of the substrate and product can easily poison the metal catalyst. Most recently, we found that the cationic ruthenium complexes of chiral monotosylated diamine<sup>8</sup> are highly effective catalysts for asymmetric hydrogenation of various N-containing heteroarenes.<sup>9</sup> In particular, this catalytic system has been demonstrated to be highly efficient for the asymmetric hydrogenation of challenging polycyclic 1,10-phenanthrolines.<sup>9c</sup> Encouraged by these results, we report herein a ruthenium-catalyzed asymmetric hydrogenation of phenanthridines with high enantioselectivity for the first time.

In the initial experiment, 6-methylphenanthridine **1a** was chosen to be hydrogenated with (*R,R*)-**3a** in THF under 50 atm of H<sub>2</sub> (Table 1). It was found that **1a** could be hydrogenated at 50 °C, giving the desired product in full conversion but with only 5% ee (Table 1, entry 1). Encouraged by this initial result and our previous reports,<sup>10</sup> the counteranion effect of catalyst was first examined. Interestingly, the enantioselectivity was influenced by the counteranions significantly (entries 1–6). The highest enantioselectivity was achieved by using catalyst (*R,R*)-**3f** with a bipolPO<sub>2</sub> anion, albeit with a lower yield. Subsequently, several conventional organic solvents were

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Table 1. Optimization of Conditions for Asymmetric Hydrogenation<sup>a</sup>


X = OTf (a); BF<sub>4</sub> (b); PF<sub>6</sub> (c); SbF<sub>6</sub> (d); BAfF (e);  
 bipolPO<sub>2</sub> (f) (PhO)<sub>2</sub>PO<sub>2</sub> (g) (R)-binolPO<sub>2</sub> (h) (S)-binolPO<sub>2</sub> (i)

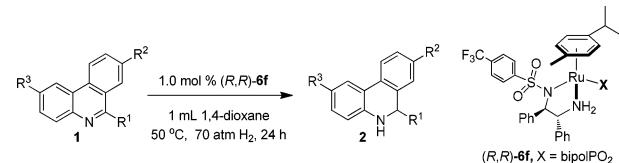
(R,R)-3: R<sup>1</sup> = CH<sub>3</sub>  
 (R,R)-4: R<sup>1</sup> = 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>  
 (R,R)-5: R<sup>1</sup> = 2,4,6-(iPr)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>  
 (R,R)-6: R<sup>1</sup> = 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>

entry	catalyst	anion [X] <sup>-</sup>	solvent	conv <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	(R,R)-3a	OTf	THF	>99	5
2	(R,R)-3b	BF <sub>4</sub>	THF	>99	7
3	(R,R)-3c	PF <sub>6</sub>	THF	>99	19
4	(R,R)-3d	SbF <sub>6</sub>	THF	>99	37
5	(R,R)-3e	BAfF	THF	>99	10
6	(R,R)-3f	bipolPO <sub>2</sub>	THF	85	66
7	(R,R)-3f	bipolPO <sub>2</sub>	MeOH	92	4
8	(R,R)-3f	bipolPO <sub>2</sub>	DCM	92	7
9	(R,R)-3f	bipolPO <sub>2</sub>	toluene	91	56
10	(R,R)-3f	bipolPO <sub>2</sub>	DME	85	65
11	(R,R)-3f	bipolPO <sub>2</sub>	1,4-dioxane	94	71
12	(R,R)-4f	bipolPO <sub>2</sub>	1,4-dioxane	88	86
13	(R,R)-5f	bipolPO <sub>2</sub>	1,4-dioxane	72	56
14	(R,R)-6f	bipolPO <sub>2</sub>	1,4-dioxane	92	89
15	(R,R)-4g	(PhO) <sub>2</sub> PO <sub>2</sub>	1,4-dioxane	95	75
16	(R,R)-4h	(R)-binolPO <sub>2</sub>	1,4-dioxane	88	87
17	(R,R)-4i	(S)-binolPO <sub>2</sub>	1,4-dioxane	93	80
18 <sup>d</sup>	(R,R)-6f	bipolPO <sub>2</sub>	1,4-dioxane	>99	89

<sup>a</sup>Reaction conditions: **1a** (0.2 mmol) in solvent (1 mL), (R,R)-Ru (1.0 mol %), H<sub>2</sub> (50 atm), stirred at 50 °C for 24 h. DCM = dichloromethane; DME = ethylene glycol dimethyl ether. <sup>b</sup>The conversions were determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixture. <sup>c</sup>The enantiomeric excesses were determined by HPLC with a chiral OD-H column. <sup>d</sup>H<sub>2</sub> (70 atm), stirred at 50 °C for 24 h.

investigated (entries 6–11). It was found that ether solvents, such as THF, DME, and 1,4-dioxane, gave high enantioselectivities. To further improve the enantioselectivity, a variety of catalysts were screened in 1,4-dioxane (entries 11–15), and (R,R)-6f was found to be optimal in terms of both reactivity and enantioselectivity (entry 14). Notably, the chirality of the counteranion slightly influenced the enantioselectivity (entries 16 and 17). In addition, the enantioselectivity of the reaction was found to be insensitive to hydrogen pressure, and full conversion was obtained under 70 atm of H<sub>2</sub> (entry 18). However, increasing the reaction temperature resulted in a remarkable decrease in enantioselectivity (see the Supporting Information, Table S1).

Under the optimal reaction conditions (Table 1, entry 18), a variety of phenanthridine derivatives were efficiently hydrogenated with good to excellent enantioselectivities (Table 2). Considering the possible effect of substituents on the enantioselectivity, we first investigated the asymmetric hydrogenation of several 6-methyl-substituted phenanthridine derivatives bearing different groups (Table 2, entries 1–6). It was found that the enantioselectivity was more sensitive to the

Table 2. Asymmetric Hydrogenation of 6-Substituted Phenanthridines Catalyzed by (R,R)-6f<sup>a</sup>


(R,R)-6f, X = bipolPO<sub>2</sub>

entry	R <sup>1</sup> /R <sup>2</sup> /R <sup>3</sup>	yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	CH <sub>3</sub> /H/H	90 (2a)	89 (–)
2	CH <sub>3</sub> /H/F	91 (2b)	77 (–)
3	CH <sub>3</sub> /H/CH <sub>3</sub>	89 (2c)	75 (–)
4	CH <sub>3</sub> /F/H	88 (2d)	86 (–)
5	CH <sub>3</sub> /CH <sub>3</sub> /H	92 (2e)	91 (–)
6	CH <sub>3</sub> /OCH <sub>3</sub> /H	89 (2f)	91 (R)
7	Et/OCH <sub>3</sub> /H	87 (2g)	90 (–)
8	<i>n</i> -Pr/OCH <sub>3</sub> /H	86 (2h)	89 (–)
9	<i>n</i> -pentyl/OCH <sub>3</sub> /H	88 (2i)	91 (–)
10	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> /OCH <sub>3</sub> /H	84 (2j)	89 (–)
11	4-FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> /OCH <sub>3</sub> /H	90 (2k)	92 (–)
12	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> /OCH <sub>3</sub> /H	92 (2l)	89 (–)
13	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> /OCH <sub>3</sub> /H	91 (2m)	92 (–)
14	3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> /OCH <sub>3</sub> /H	90 (2n)	92 (–)
15	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> /OCH <sub>3</sub> /H	86 (2o)	89 (–)
16	–CH=CHC <sub>6</sub> H <sub>5</sub> /OCH <sub>3</sub> /H	92 (2p)	90 (–)
17	C <sub>6</sub> H <sub>5</sub> /H/H	NR	

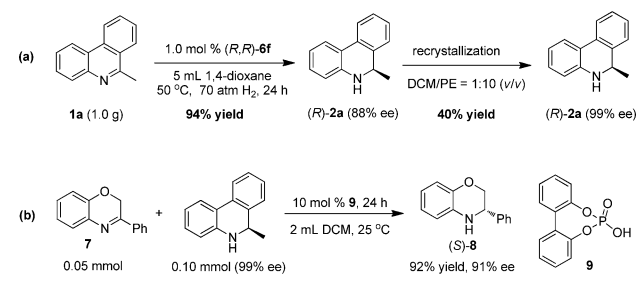
<sup>a</sup>Reaction conditions: **1** (0.2 mmol) in 1,4-dioxane (1 mL), (R,R)-6f (1.0 mol %), H<sub>2</sub> (70 atm), stirred at 50 °C for 24 h. <sup>b</sup>Isolated yield. <sup>c</sup>The enantiomeric excesses were determined by chiral HPLC analysis. The absolute configuration of **2f** was determined to be *R* based on single-crystal X-ray analysis of the corresponding tosylated derivative **10** (Scheme S1, Supporting Information).

position than the electronic property of the substituents. When substrates bearing methyl and fluoro groups at the 2-position were used, low enantioselectivity was observed (entries 2 and 3). The highest ee value was achieved in the hydrogenation of **1f** bearing a methoxyl group at the 8-position. Then, a variety of 6-substituted phenanthridine derivatives bearing 8-methoxyl groups were hydrogenated. Generally, 6-alkyl-substituted 8-methoxyphenanthridines (**1f–i**) were hydrogenated smoothly regardless of the length of the chain (entries 6–9). Moreover, the electronic properties of the substituents at the *para*, *meta*, even *ortho* position of the phenyl ring had no apparent effect on enantioselectivity (**1k–o**). Interestingly, hydrogenation of 6-styryl-substituted phenanthridine **1p** proceeded smoothly under identical conditions, and the conjugated double bond was also hydrogenated. For the 6-phenyl-substituted substrate (**1q**), hydrogenation could not take place.

To explore the potential application of this synthetic protocol in the practical synthesis of chiral 5,6-dihydrophenanthridines, a gram-scale experiment was carried out (Scheme 1a). The asymmetric hydrogenation of **1a** performed on a gram scale (1.0 g) afforded the chiral (*R*)-**2a** in 94% yield with 88% ee. After a single recrystallization from DCM and petroleum ether (PE), enantiomerically pure (*R*)-**2a** with 99% ee could be obtained.

Considering that chiral 5,6-dihydrophenanthridines have the potential to serve as a new kind of chiral NAD(P)H models,<sup>7,11</sup> we chose the organocatalytic transfer hydrogenation of 3-phenyl-2*H*-1,4-benzoxazine as the model reaction (Scheme 1b). It was found that the reaction proceeded smoothly in the presence of 10 mol % of racemic phosphate acid and 2 equiv of

### Scheme 1. Scale-up Synthesis of Chiral 5,6-Dihydrophenanthridine and Application in the Organocatalytic Transfer Hydrogenation of 3-Phenyl-2H-1,4-benzoxazine



chiral (R)-2a in DCM at room temperature, producing (S)-8 in 92% yield with 91% ee.

In conclusion, we have developed the first asymmetric hydrogenation of 6-substituted phenanthridines by using phosphine-free chiral cationic ruthenium diamine catalysts with up to 92% ee. The counteranion was found to be critically important for the high enantioselectivity. This new protocol thus provides an easy path for the preparation of optically pure 5,6-dihydrophenanthridines, which are key substructures in biologically active molecules and pharmaceuticals.

#### ■ ASSOCIATED CONTENT

##### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00419.

Experimental procedures, synthesis of the starting materials, and compound characterization data (PDF)  
X-ray data for derivative of chiral compound 2f (CIF)

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##### Notes

The authors declare no competing financial interest.

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