

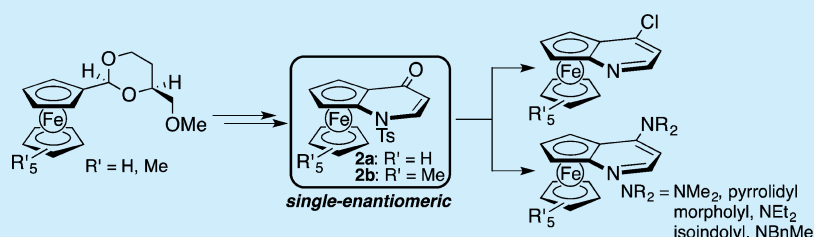
Enantioselective Synthesis of Planar-Chiral Ferrocene-Fused 4-Pyridones and Their Application in Construction of Pyridine-Based Organocatalyst Library

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S Supporting Information



ABSTRACT: A couple of planar-chiral ferrocene-fused 4-pyridone derivatives **2a** and **2b** were synthesized in enantiomerically pure form by scalable asymmetric transformations. Pyridones **2** are versatile precursors to various ferrocene-fused pyridine derivatives, which are useful nucleophilic asymmetric organocatalysts.

Derivatives of 4-dialkylaminopyridine (DAAP) are widely utilized nucleophilic catalysts in various organic transformations.¹ Their application in asymmetric synthesis has been a recent trend and many efforts have been made to develop effective chiral variants of DAAPs.^{2,3} Arguably the most successful chiral DAAPs reported so far are planar-chiral ferrocene-fused pyridine derivatives **1**, which have been developed by G. C. Fu since 1996.^{4,5} Although compounds **1** have showed excellent enantioselectivity in a wide range of asymmetric reactions,^{4,5} applications of these elegant molecules have been rather limited⁶ probably due to the complicated synthesis (Scheme 1). Two apparent drawbacks in Fu's synthetic

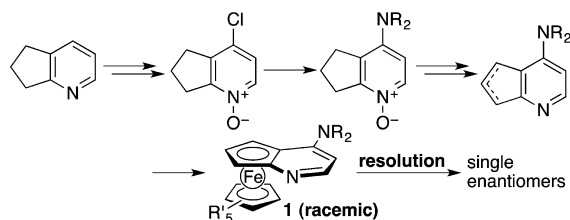
derivative of **1** with a different 4-substituent needs to be prepared as a respective racemate through the independent reaction sequence, and naturally, the last stage chiral resolution of each compound is inevitable.

In this letter, we report the enantioselective synthesis of planar-chiral 4-pyridones **2**. Compounds **2**, which were obtained in enantiomerically pure form in multigram scales, are excellent and versatile precursors to **1**. The newly developed detosylative amination of **2** provided diverse **1**, including previously unreported species, as single-enantiomers. Thus, the library of the planar-chiral nucleophilic organocatalysts could be effectively constructed.

Our strategy for asymmetric synthesis of **1** consists of three key steps: (i) introduction of proper substituents at the 1- and 2-positions of a ferrocene platform with controlling its planar-chirality, (ii) construction of a six-membered *N*-heterocycle by a ring-closure reaction, and (iii) aromatization of the *N*-heterocycle into a pyridine ring with introduction of a proper substituent at the 4-position (Scheme 2, top).

To realize the idea, planar-chiral pyridones **2** were designed as versatile precursors to **1** (Scheme 2, bottom). Pyridones **2** possess a modifiable carbonyl group at the proper position, and the last-stage introduction of a 4-amino group would make our synthesis flexible, and thus, construction of the library of **1** might be realized. Olefin metathesis was chosen for the cyclization step since we have experienced utilizing RCM for construction of

Scheme 1. Reported Fu's Original Synthesis of Planar-Chiral Ferrocene-Fused 4-Dialkylaminopyridines **1**



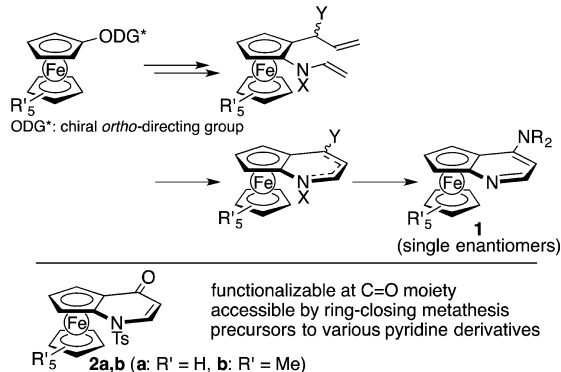
protocols are (i) necessity of the last stage chiral resolution of preformed racemic **1**,^{4b,c,7} and (ii) limited diversity with respect to a substituent at the 4-position in the pyridine ring. An amino group at the 4-pyridyl position, which plays important roles in controlling the activity/selectivity of DAAPs,⁸ was introduced in the middle stage of the synthetic sequences. This means that each

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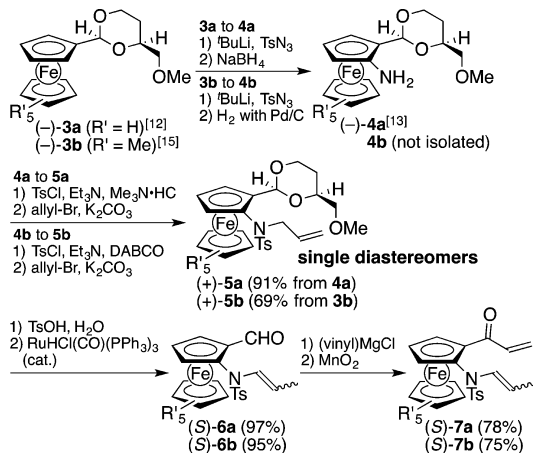
Scheme 2. Strategy for Asymmetric Synthesis of Planar-Chiral Ferrocene-Fused 4-Dialkylaminopyridines 1



aromatic compounds^{9,10} as well as for modification of various ferrocene substrates.¹¹

At the outset, the synthesis of **2a** that is with a CpFe moiety was examined. Kagan's acetal (–)-**3a**¹² was converted to (–)-**4a** in >98% de as reported.¹³ Tosylation and allylation of (–)-**4a** afforded amide (+)-**5a** in 91% yield as a single diastereomer after chromatographic purification. Deprotection of the chiral acetal moiety followed by the Ru-catalyzed olefin isomerization¹⁴ gives enamide (S)-**6a** in 97% yield as a mixture of (*E*)- and (*Z*)-isomers (*E/Z* = 10/3). The formyl group in (S)-**6a** was transformed to an acrolyl group by the sequential vinylation/oxidation, and (S)-**7a**, which was a RCM substrate, was obtained in 78% yield with retention of enantiomeric homogeneity with respect to the planar-chirality. Although (S)-**7a** was an inseparable mixture of the (*E*)- and (*Z*)-isomers, this was not a drawback because the RCM of both (*E*)- and (*Z*)-**7a** would lead to the same product (**2a**) with elimination of propene (Scheme 3).

Scheme 3. Enantio-/Diastereoselective Synthesis of Planar-Chiral Ferrocene-Fused Enone-Enamide Derivatives (S)-7

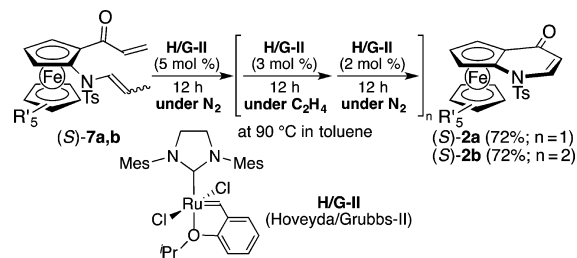


The synthesis of Cp* analogue (S)-**7b** could be achieved in a similar manner with slight modifications. Chiral acetal (–)-**3b**¹⁵ was converted to **4b** via diastereoselective azidation and the Pd-catalyzed hydrogenation. With the more electron-donating Cp* ligand, aminoferrocene **4b** is more susceptible to air-oxidation, and thus, crude **4b** was converted to (+)-**5b** without purification. The NMR analysis of (+)-**5b** showed the isolated sample being single-diastereomeric. The transformation of (+)-**5b** into (S)-**7b**

was carried out as above, and (S)-**7b** was isolated as deep-red solid as a mixture of (*E*)- and (*Z*)-isomers (*E/Z* = 5/2).

Next, the ring-closing metathesis reactions of (S)-**7a/7b** were examined. The two olefin moieties in (S)-**7** are an electron deficient enone and a nitrogen-bound internal olefin, which are unfavorable situations for facile RCM. The Hoveyda/Grubbs-II catalyst¹⁶ was a catalyst of choice for the RCM. After optimizing the conditions, (S)-**2a** and (S)-**2b** were obtained both in 72% yields (Scheme 4; see Supporting Information for details). The

Scheme 4. Ring-Closing Metathesis of (S)-7 Forming (S)-2



present protocol for preparing (S)-**2** is scalable, and synthesis of (S)-**2b** on a multigram scale was accomplished without any difficulties.

Single crystals of (–)-**2b** were grown from pentane/dichloromethane as deep red plates. The X-ray crystallography revealed that the compound was single enantiomeric, and the absolute configuration of (–)-**2b** was determined to be (*S*), which is consistent with the stereochemistry reported on the diastereoselective lithiation of (–)-**3b** (Figure 1, see Supporting Information for details).^{12,15}

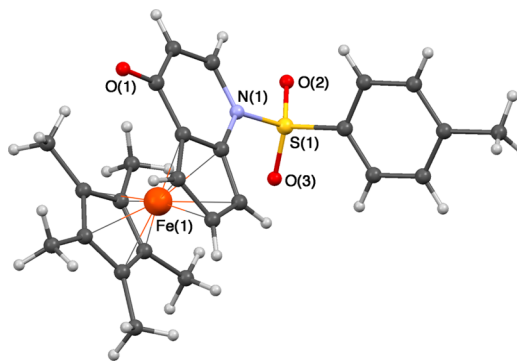
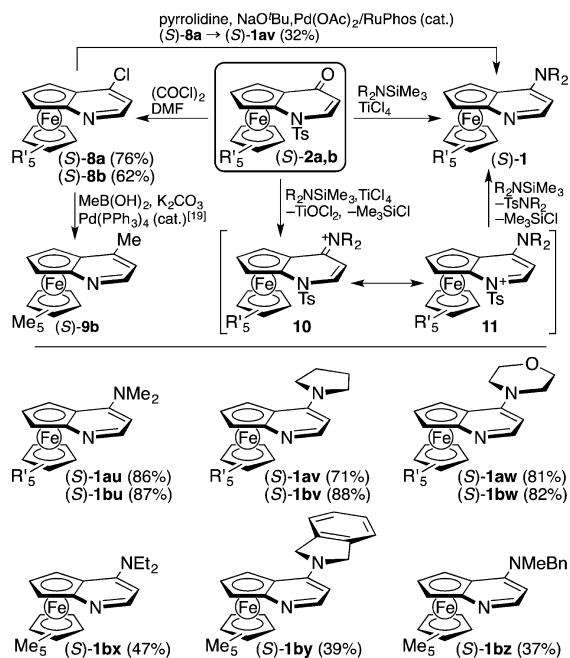


Figure 1. Ball-and-stick drawing of the single-crystal X-ray structure of (S)-(-)-**2b** with selected atom numbering.

Planar-chiral (S)-**2a/2b** were versatile precursors to various pyridine derivatives (Scheme 5). Treatment of (S)-**2a/2b** with a mixture of oxalyl chloride and DMF gave the corresponding 4-chloropyridine derivatives (S)-**8a** or (S)-**8b** in 76% or 62% yields, respectively.¹⁷ The C–Cl moiety in (S)-**8** could be modified by the palladium-catalyzed reactions. For example, the Buchwald–Hartwig amination of (S)-**8a** with pyrrolidine afforded (S)-**1a** in 32% yield.¹⁸ The preparation of *rac*-**8b** and its conversion to 4-methylpyridine derivative *rac*-**9b** via the Suzuki–Miyaura coupling reaction (94% yield) were described previously.¹⁹ However, *rac*-**9b** needed to be resolved into the two enantiomers using the chiral HPLC prior to its catalytic application. The same reaction starting with single-enantiomeric (S)-**8b** should allow us direct access to enantiomerically pure (S)-**9b**.

Scheme 5. Conversion of Pyridones 2 to Pyridine Derivatives



The direct conversion of **2** into various DAAP derivatives (**S**)-**1** was achieved by the reaction with an appropriate *N*-trimethylsilylamine in the presence of titanium tetrachloride in good yields.²⁰ For the desotylative amination reaction, two equivalents of *N*-silylamine were required. The process most likely proceeded via an initial formation of iminium species **10**, which also existed in different resonance form **11**. The subsequent reaction of *N*-tosylpyridinium **11** with R_2NSiMe_3 afforded the corresponding **1** together with tosylamide $TsNR_2$, which was indeed isolated from the reaction mixture. DMAP (**1au**, **1bu**), PPY (**1av**, **1bv**), morpholyl (**1aw**, **1bw**), and diethylamino (**1bx**) derivatives were prepared in good to excellent yields by the reaction using the corresponding commercial silylamines. The silylamine species generated in situ from isoindoline, *i*PrMgBr, and Me_3SiCl could be used for the present reaction as well, and **1by** was obtained in 39% yield. The desotylative amination of (**S**)-**2b** could be operative without using silylamines, and the combination of *N*-benzylmethylamine, $TiCl_4$, and DBU furnished (**S**)-**1bz**, which is with the unsymmetric 4-dialkylamino substituent, in 37% yield. It should be emphasized that all the transformations shown in Scheme 5 are enantioretentive. Whereas (**S**)-**2a** and (**S**)-**2b** obtained by our method are enantiomerically pure, all the other planar-chiral ferrocene derivatives in Scheme 5 are also single-enantiomeric, i.e., we could have established the divergent process preparing a library of various planar-chiral pyridine-based nucleophilic organocatalysts in enantiomerically pure forms without chiral resolution.

The library of (**S**)-**1** was examined in the two prototypical asymmetric reactions. The first one is the addition reaction of 2-*t*-Bu-phenol (**13**) to ethyl(*p*-tolyl)ketene (**12**),^{4i,21} and the results are summarized in Table 1. With the exception of **1aw** (entry 3), all the other ferroc-pyridine derivatives showed good catalytic activity for the reaction giving ester **14** in excellent yields. The catalysts with an η^5 - C_5H_5 (**1au**, **1av**, and **1aw**) moiety showed the modest enantioselectivity of 57% ee at most (entries 1–3). With the sterically more demanding Cp^* ligand in place of Cp in **1**, the enantioselectivity was greatly improved ranging 79–

Table 1. Enantioselective Addition of *o*-*t*-Bu-Phenol to Ethyl(*p*-tolyl)ketene Catalyzed by (**S**)-**1**^a

entry	(S)- 1	yield (%) ^b	% ee ^c
1	1au	89	52
2	1av	88	57
3	1aw	57	12
4	1bu	92	79
5	1bv	90	92
6	1bw	84	79
7	1bx	90	90
8	1by	92	88
9	1bz	89	87

^aThe reaction was carried out in toluene at 23 °C in the presence of catalyst (**S**)-**1** (3 mol %). The absolute configuration of **14** was deduced by comparison with the reported results [ref 4i]. ^bIsolated yield by silica gel chromatography. ^cDetermined by HPLC analysis on a chiral stationary phase (see the Supporting Information for details).

92% ee (entries 4–9). Among the library of the pyridine organocatalysts prepared, those with the pyrrolidyl (**1bv**) or the diethylamino (**1bx**) substituent afforded (**R**)-**14** in greater than 90% ee (entries 5 and 7).

The second asymmetric reaction examined is the kinetic resolution of racemic alcohol **15**.^{4b} The acetylation of *rac*-**15** with acetic anhydride proceeds in an enantioselective fashion in the presence of (**S**)-**1** (4 mol %) to give ester (**S**)-**16** and recovered (**R**)-**15** (Table 2). All the ferroc-pyridines (**1bu**–**1by**) showed

Table 2. Enantioselective Acetylation of *rac*-**15** Catalyzed by (**S**)-**1**^a

entry	(S)- 1	conv (%) ^b	% ee of 16 ^c	% ee of 15 ^c	<i>s</i> -factor ^d
1	1bu	65	41 (S)	75 (R)	5.0
2	1bv	62	43 (S)	70 (R)	5.0
3	1bw	66	41 (S)	78 (R)	5.3
4	1bx	70	39 (S)	92 (R)	6.7
5	1by	60	40 (S)	61 (R)	4.2

^aThe reaction was carried out in ether at 20 °C in the presence of catalyst (**S**)-**1** (4 mol %). ^bDetermined by ¹H NMR analysis. ^cDetermined by HPLC analysis on a chiral stationary phase (see the Supporting Information for details). The absolute configurations of **16** and recovered **15** were determined by comparison with the reported results [ref 4b]. ^dCalculated based on a first-order equation [ref 22].

moderate enantioselectivity with the *s*-factors ranging 4.2–6.7. The highest enantioselectivity was recorded with (**S**)-**1bx** (entry 4), which is the newly prepared species by the present study. This is the clear-cut advantage of having the library of the asymmetric catalysts.

In summary, we have established the synthesis of planar-chiral ferrocene-fused 4-pyridone derivatives **2a** and **2b** both in enantiomerically pure forms. Our synthetic method is scalable and the single-enantiomeric pyridones could be obtained in a multigram scale. Compounds **2** could be converted into various

enantiomerically pure ferrocene-fused pyridine derivatives **1** via enantioselective transformations, and the library of the planar-chiral pyridine-based nucleophilic organocatalysts could be obtained.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures, compound characterization data, and crystallographic data of (S)-(-)-**2b** (CIF file). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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