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

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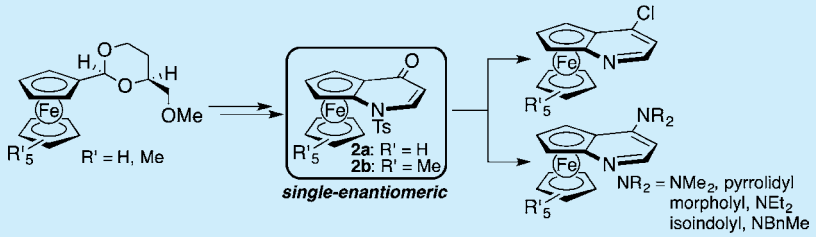
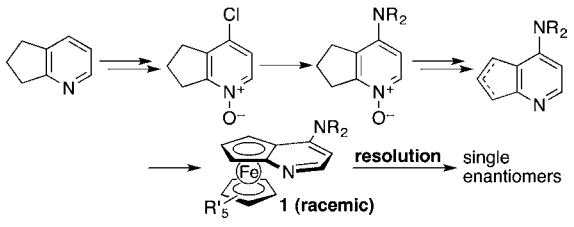
Supporting Information



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 limited[6] probably due to the complicated synthesis (Scheme 1). Two apparent drawbacks in Fu's synthetic

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 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

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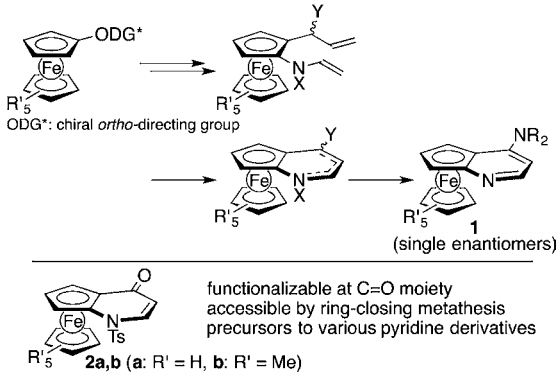
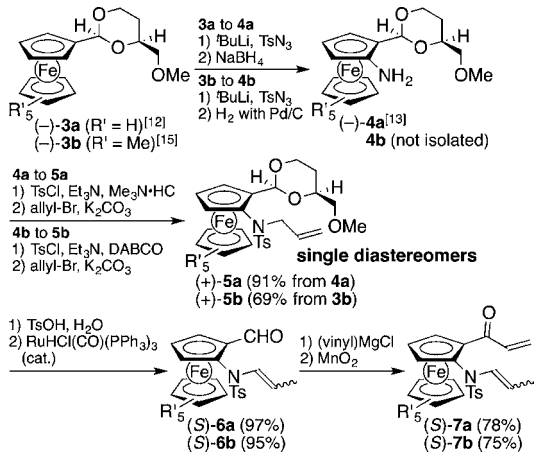
Scheme 2. Strategy for Asymmetric Synthesis of Planar-Chiral Ferrocene-Fused 4-Dialkylaminopyridines 1



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 isomerization[14] 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 acroyl 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).

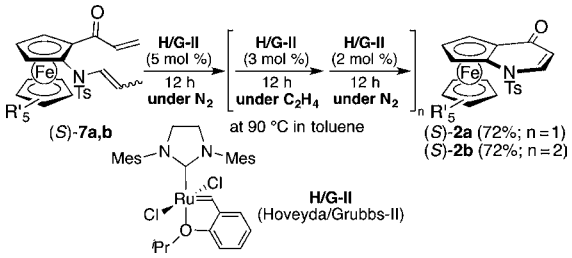
Scheme 3. Enantio-/Diastereoselective Synthesis of Planar-Chiral Ferrocene-Fused Enone-Enamide Derivatives (*S*)-7



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 catalyst[16] 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]

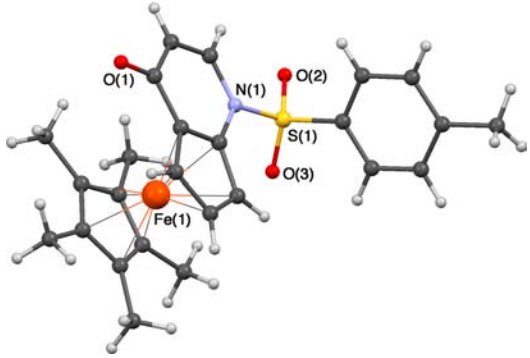


Figure 1. Ball-and-stick drawing of the single-crystal X-ray structure of (*S*)-(−)-**2b** with selected atom numbering.

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*)-**1av** 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**.

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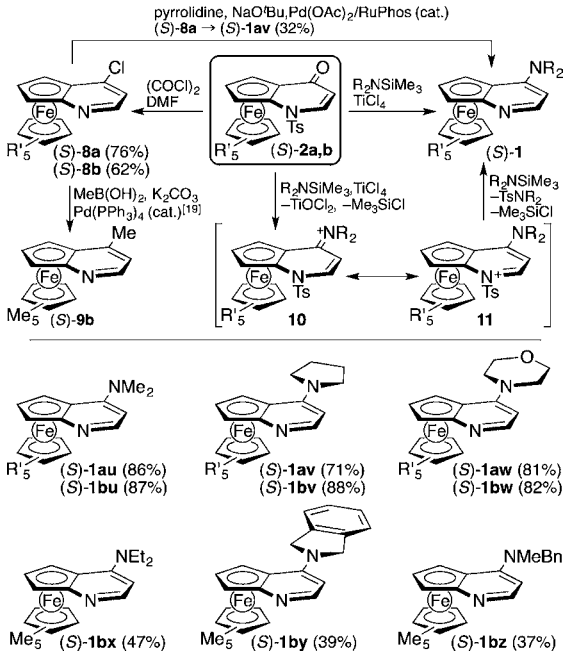
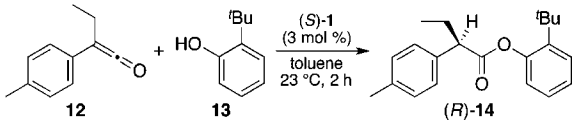
Scheme 5. Conversion of Pyridones 2 to Pyridine Derivatives



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 detosylative 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 detosylative 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 ferroco-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 79–92% 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).

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

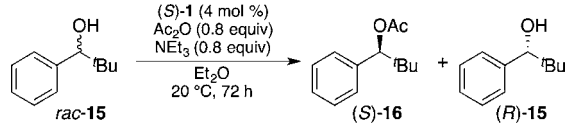


entry	(*S*)-**1**	yield (%)[b]	% ee[c]
1	**1au**	89	52
2	**1av**	88	57
3	**1aw**	57	12
4	**1bu**	92	79
5	**1bv**	90	92
6	**1bw**	84	79
7	**1bx**	90	90
8	**1by**	92	88
9	**1bz**	89	87

[a]The 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]. [b]Isolated yield by silica gel chromatography. [c]Determined by HPLC analysis on a chiral stationary phase (see the Supporting Information for details).

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 ferroco-pyridines (**1bu**–**1by**) showed 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.

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]	*s*-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

[a]The reaction was carried out in ether at 20 °C in the presence of catalyst (*S*)-**1** (4 mol %). [b]Determined by ^{1}H NMR analysis. [c]Determined 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]. [d]Calculated based on a first-order equation [ref 22].

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

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enantiomerically pure ferrocene-fused pyridine derivatives **1** via enantioretentive 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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