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Versatile and Enantioselective Preparation of Planar-Chiral Metallocene-Fused 4-Dialkylaminopyridines and Their Application in Asymmetric Organocatalysis

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Abstract: A series of ferrocene-fused planar-chiral *N*-tosyl-4-pyridones (*S*)-**2b-d** were prepared in enantiomerically pure forms. Starting with the chiral ferrocenyl acetals, 1-[(2*S*,4*S*)-4-methoxymethyl-1,3-dioxan-2-yl]-1',2',3',4',5'-R_5-ferrocenes ((–)-**3b**, R = Me; (–)-**3c**, R = Ph; (–)-**3d**, R = Bn), *N*-tosylamino and formyl groups were introduced at the 1- and 2-positions of the ferrocene cores in (*S*)-**11b-d** with control of the planar chirality. After the reaction with

ethynylmagnesium bromide, generated propargyl alcohol derivatives (*S*)-**17** were treated with MnO_2 and catalytic TBAI to give the planar-chiral pyridones by the iodide-catalyzed cyclization. This method is highly practical with a shorter and higher-yield sequence without using noble metal catalysts. Planar-chiral ferroco-pyridones (*S*)-**2b-d** were reacted with various $Me_3Si\text{-}NR'_2$ to give a library of ferrocene-fused 4-dialkylaminopyridines ((*S*)-**1**, DAAPs) in high yields as single-enantiomers by the detosylative amination. The cymantrene-fused DAAPs were also prepared in the same way. The library of the chiral DAAPs were examined in the two asymmetric reactions as organocatalysts, and some newly prepared Fc-DAAPs showed better enantioselectivity than the known species.

Keywords: planar-chiral; ferrocene; cymantrene; enantioselective; 4-pyridone; 4-dialkylaminopyridine; organocatalyst; cyclization

Introduction

Ferrocene is a cylindrical compound with unique three-dimensional properties.[1,2] Introduction of two different substituents at the 1- and 2-positions of an Fe(II)-bound η^5-cyclopentadienyl ligand breaks the symmetry to induce planar chirality in the molecule (Figure 1, left).[3] The ferrocene-based planar chirality has been proven to be useful chiral scaffolds in asymmetric synthesis, and various such ferrocene derivatives have been utilized in a wide range of asymmetric reactions as chiral ligands[4] and chiral catalysts.[5,6]

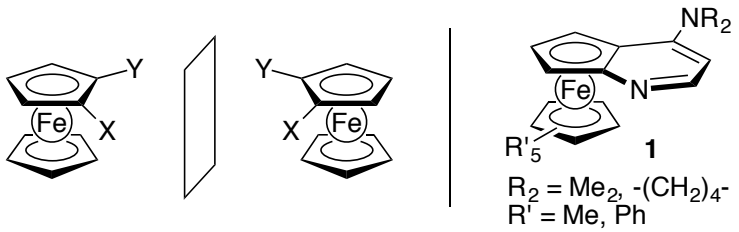
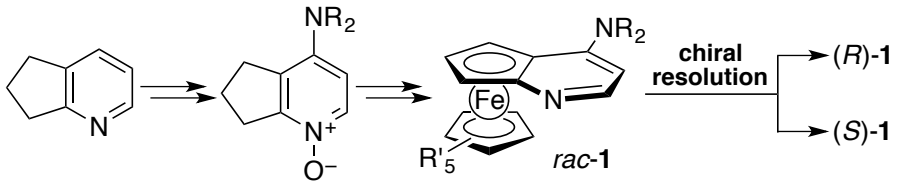


Figure 1. Enantiomeric pair of 1,2-disubstituted ferrocene (left) and Fu's ferrocene-fused planar-chiral 4-dialkylaminopyridines **1** (right).

In 1990s, G. C. Fu employed this design concept for desymmetrizing flat-shaped *N*-heteroarenes, and since then various ferrocene-fused 4-dialkylaminopyridines (Fc-DAAPs; **1**; Figure 1, right) were prepared and applied in asymmetric organocatalysis. Among many chiral 4-dialkylaminopyridine derivatives reported so far,[7,8] Fc-DAAPs are arguably the most successful compounds.[6] And indeed, **1** showed excellent enantioselectivity in a variety of asymmetric transformations.[9] In spite of the exceptional catalytic properties of **1**, applications of these stylish molecules have been rather limited[9,10] probably due to their limited availability. The synthetic sequence developed by Fu is shown in Scheme 1. Two major drawbacks in this synthetic protocol are (i) necessity of the late stage chiral resolution of preformed racemic **1**, and (ii) limited diversity with respect to a substituent at the 4-position in the pyridine ring.[9b,9c,11] A dialkylamino group at the 4-pyridyl position, which plays important roles in controlling the catalytic activity/selectivity of chiral DAAPs,[12] 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 late stage chiral resolution of each compound is essential.

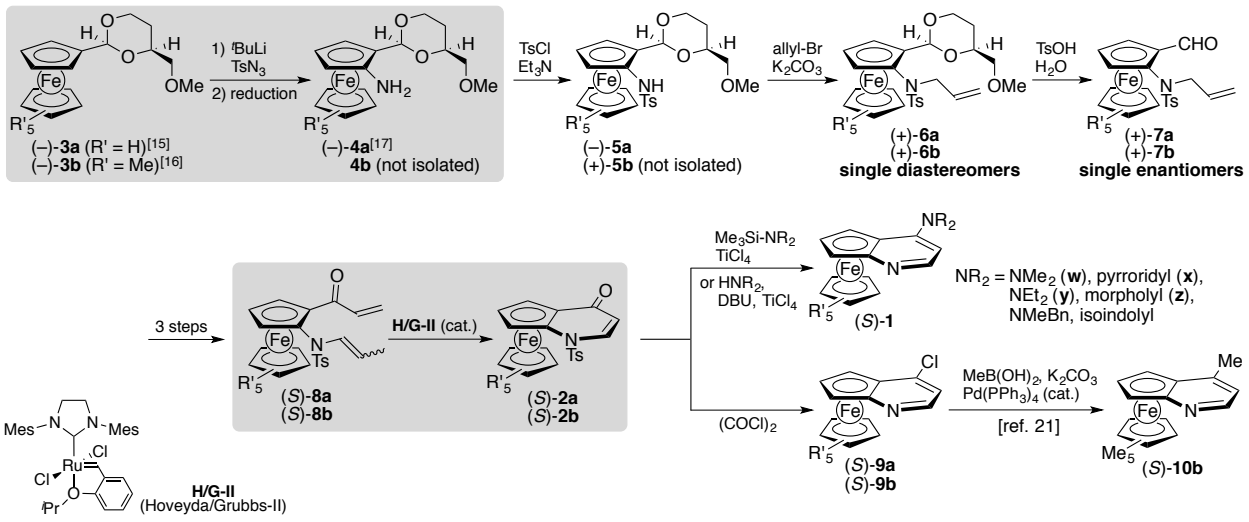


Scheme 1. Fu's Original Synthesis of *rac*-**1** and Enentiomeric Resolution.

In 2015, we reported an enantioselective synthesis of Fc-DAAPs and related compounds, which *partly* overcame the drawbacks in the Fu's original synthesis of **1** (Scheme 2).[13] The three features of our synthetic strategy are: (i) introduction of proper substituents at the 1- and 2-positions of a ferrocene platform with controlling its planar chirality utilizing a chiral *ortho*-directing group (**3** to **4** in Scheme 2),[14] (ii) construction of the ferrocene-fused 4-pyridones by the ring-closing metathesis reaction (**8** to **2** in Scheme 2), and (iii) the late stage introduction of various substituents at the 4-position of the ferrocene-fused pyridines (**2** to **1**, **9**, and **10**). The chiral 1,3-dioxan-2-yl group in **3**, developed by Kagan and his coworkers,[15-17] is a powerful chiral directing group for the highly diastereoselective lithiation of **3** (>99% de). Planar-chiral 4-pyridones **2**, obtained in essentially enantiomerically pure forms, are versatile synthetic intermediates, and they could be converted to the various pyridine derivatives with retention of the planar chirality in **2**. An analogous synthetic strategy was applied to the synthesis of metallocene-fused planar-chiral phospholes recently.[18]

Although the synthetic method in Scheme 2 provided a library of the planar-chiral pyridine-based nucleophilic organocatalysts, including previously unknown species, without chiral resolution, it still had room for further improvement. For example, the reaction sequence in Scheme 2 is somewhat lengthy and some steps require the use of expensive noble metal catalysts, such as the Hoveyda/Grubbs-II catalyst,[19] with relatively high catalyst loading. Furthermore, this

"first-generation synthesis" shows severe steric hindrance. The method can be used for the preparation of the Cp- and Cp*-derivatives (R' = H or Me), but the corresponding η^5-C_5Ph_5-analogues were not obtained in the same way (vide infra). It should be mentioned that the C_5H_5-derivatives of **1** are synthetically far less important due to the lower-enantioselectivity on their applications in asymmetric catalysis, and the sterically demanding η^5-C_5Ph_5-analogues show much better performance in many reactions.[9b,d,e,m]



Scheme 2. Enantioselective Synthesis of Ferrocene-Fused 4-Pyridones **2** and Pyridine Derivatives **1**, **9**, and **10**[21]: "First-Generation Synthesis" Using Ruthenium-Catalyzed Ring-Closing Metathesis for Cyclization.[13]

With the background mentioned above, we started the present studies with intention to overcome the limitations of the first generation synthesis of **1** (Scheme 2). The improved "second generation synthesis" developed in this study is much shorter (i. e., more effective) and much less costly without using the expensive noble metal catalysts. And more importantly, the newly

developed synthesis can provide sterically demanding analogues of Fc-DAAPs which are with an (η^5-C_5Ph_5)Fe or (η^5-C_5Bn_5)Fe substructure. These bulky Fc-DAAP derivatives are synthetically more useful showing better enantioselectivity in many cases. It should be mentioned that the (η^5-C_5Bn_5)Fe derivatives are previously unknown and prepared for the first time through this study.

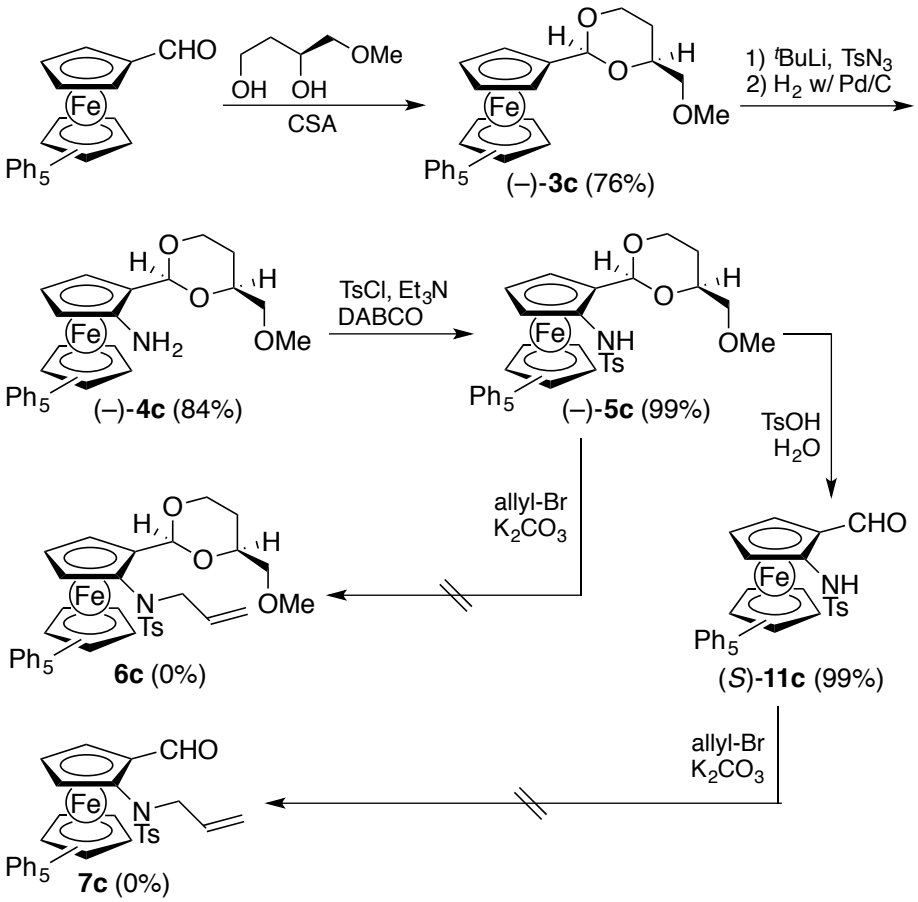
In this article, we would like to report the details of the innovative second-generation enantioselective synthesis of planar-chiral Fc-DAAPs and their application in asymmetric organocatalysis.

Results and Discussion

Unsuccessful Attempts to Prepare η^5-C_5Ph_5-Derivatives of Fc-DAAPs by First Generation Synthesis. As mentioned in the introduction section, our original method of enantioselective synthesis of Fc-DAAPs, shown in Scheme 2, works only for the η^5-C_5H_5- and η^5-C_5Me_5-derivatives, and the corresponding η^5-C_5Ph_5-derivatives could not be prepared in the same way.

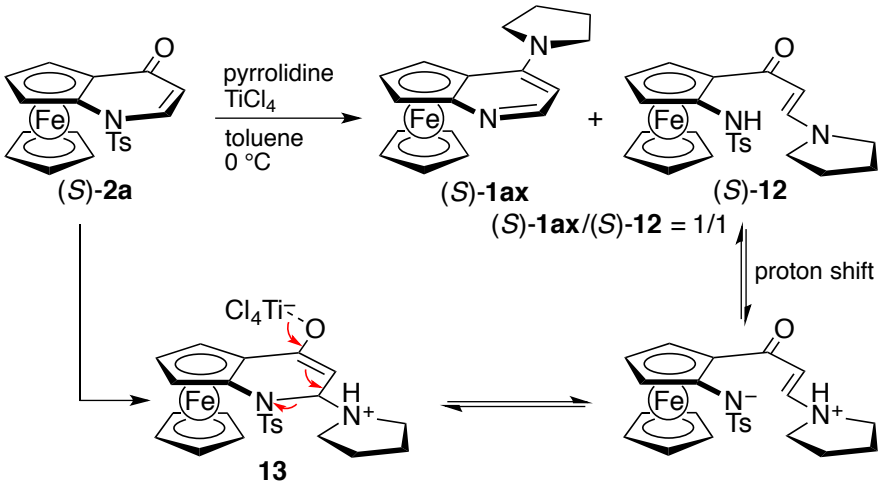
The results of the unsuccessful attempts at preparing the η^5-C_5Ph_5-derivatives are summarized in Scheme 3. Chiral acetal (–)-**3c** was prepared from 1-formyl-1',2',3',4',5'-pentaphenylferrocene[20] and (*S*)-4-methoxybutane-1,3-diol in 76% yield. Chiral (2*S*,4*S*)-4-methoxymethyl-1,3-dioxan-2-yl substituent in **3c** is an excellent chiral directing group,[15,16] and deprotonation of **3c** took place with high diastereoselectivity of >99.5% de. Lithiation of **3c** using ^{t}BuLi at –78 °C in THF followed by a reaction with tosyl azide gave the corresponding ferrocenyl azide, and subsequently the crude azide was reduced under a hydrogen atmosphere in

the presence of catalytic Pd/C to give ferrocenylamine (–)-**4c** in 84% yield (for two steps). The ^{1}H- and ^{13}C-NMR analyses of (–)-**4c** clarified the compound to be essentially diastereomerically pure. After *N*-tosylation of (–)-**4c** in >99%, *N*-allylation of (–)-**5c** was examined. To our disappointment, however, the *N*-allylation did not proceed under the conditions in Scheme 3 and desired **6c** could not be obtained. It was suspected that the robustness of (–)-**5c** toward the *N*-allylation might be ascribed to the steric hindrance by the bulky η^5-C_5Ph_5 ligand. To diminish the steric problems in (–)-**5c** as much as possible, the *N*-allylation was also examined after deprotection of the chiral 1,3-dioxanyl moiety, but the reaction on aldehyde (*S*)**-11c** did not afford *N*-allylated species **7c**. At this stage, we gave up to pursue the synthesis of the (η^5-C_5Ph_5)Fe-derivatives by the method in Scheme 2.



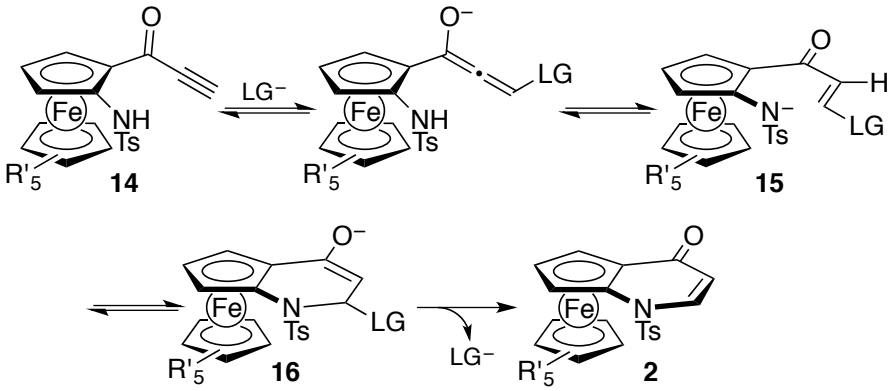
Scheme 3. Unsuccessful Attempts to Prepare Pentaphenylferrocene-Fused DAAP Derivatives by First Generation Synthesis.

Development of Transition-Metal Free Iodide-Catalyzed Cyclization Producing 4-Pyridones 2. During our investigations on the transformation of pyridone (*S*)-**2a** to pyridine (*S*)-**1ax**,[13,22] we encountered the formation of unexpected "ring-opening" product (*S*)-**12** using an equimolar mixture of pyrrolidine and titanium(IV) chloride under the unoptimized conditions. The formation of (*S*)-**12** was rationalized as depicted in Scheme 4. In the presence of Lewis-acidic $TiCl_4$, pyrrolidine attacks at the β-olefinic carbon in (*S*)-**2a** to give intermediate **13**, which subsequently eliminates the tosylamide anion to give the ring-opening product via a proton shift.



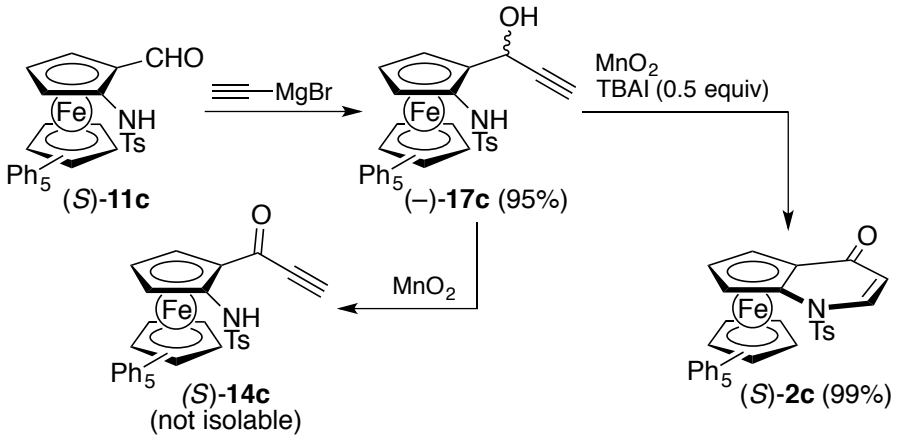
Scheme 4. Formation of Ring-Opening Product (*S*)-**12** by Reaction of Pyridone (*S*)-**2a** with Pyrrolidine in the Presence of Titanium(IV) Chloride.

On the assumption that the reaction steps between **13** and (*S*)-**12** were reversible, a transition-metal-free cyclization process producing 4-pyridones **2** was pursued (Scheme 5).[23] We envisioned that enone **15**, which possesses a potential leaving group "LG" on the β-sp^2-carbon, might undergo a cyclization providing pyridone **2** as in Scheme 5. For the success of this pyridone formation instead of the ring-opening as in Scheme 4, the LG substituent in **16** must be a better leaving group than the tosylamide moiety. Cyclization precursor **15** could be generated *in situ* by the conjugate addition of a nucleophilic LG$^-$ to ynone **14**. Whereas LG$^-$ would be regenerated at the transformation of **16** to **2**, a substoichiometric (catalytic) amount of LG$^-$ might be sufficient.



Scheme 5. Strategy for Nucleophile-Catalyzed Cyclization of 1-Propynoyl-2-*N*-tosylaminoferrocene **14**.

At the outset, this idea was examined in the synthesis of pentaphenylferroco-pyridone **2c**, which could not be prepared by our first generation synthesis as mentioned in the previous section. The results are summarized in Scheme 6. Treatment of aldehyde (*S*)-**11c**, which was prepared as in Scheme 3, with ethynylmagnesium bromide afforded propargylic alcohol (–)-**17c** in 95% yield as a diastereomeric mixture. Ynone (*S*)-**14c** could be prepared by the MnO_2-oxidation of (–)-**17c** in dichloromethane, but the compound was easily polymerized into uncharacterized gummy materials and was not isolable. Due to the susceptibility of (*S*)-**14c**, a direct conversion of (–)-**17c** into (*S*)-**2c** "in one pot" was tested. That is, propargylic alcohol (–)-**17c** was reacted with manganese(IV) oxide in the presence of a catalytic nucleophile. After an extensive survey of various nucleophiles, which include pyridine, DMAP, DABCO, triethylamine, copper(I) iodide, etc., it was found that a reaction using tetrabutylammonium iodide (TBAI; 0.5 equiv. to **17c**) proceeded cleanly to produce (*S*)-**2c** in 99% yield (see the Supporting Information for details).



Scheme 6. Iodide-Catalyzed Synthesis of Ferrocene-Fused 4-Pyridone **2c**.

Deep red crystals of (–)-**2c** was grown by slow diffusion of pentane into the concentrated dichloromethane solution of (–)-**2c**. The single-crystal X-ray crystallography revealed that the compound was a single enantiomer. The unit cell contains two independent molecules, having slightly different conformations, and the structure of one of the two crystallographically independent molecules is shown in Figure 2.[24] The absolute configuration of levorotatory **2c** was determined to be (*S*), which is consistent with the stereochemistry deduced from the diastereoselective lithiation of (–)-**3c**.[15,16] The tosyl group on N(1) takes the position opposite to the bulky η^5-C_5Ph_5 ligand avoiding steric interactions with the phenyl groups. On the other hand, the space above the carbonyl moiety of the pyridone ring remains relatively open, which may be an important issue for the conversion of **2c** to dialkylaminopyridine derivatives **1** by the reactions with trimethylsilylamines (vide infra).

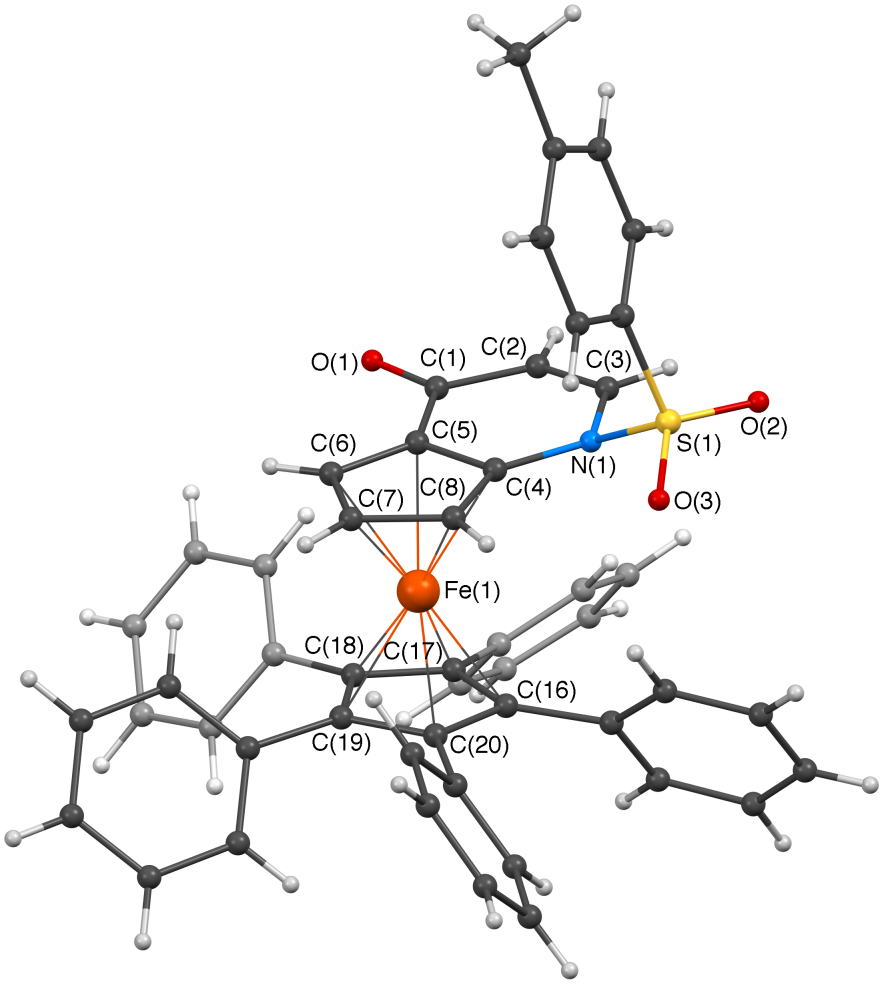
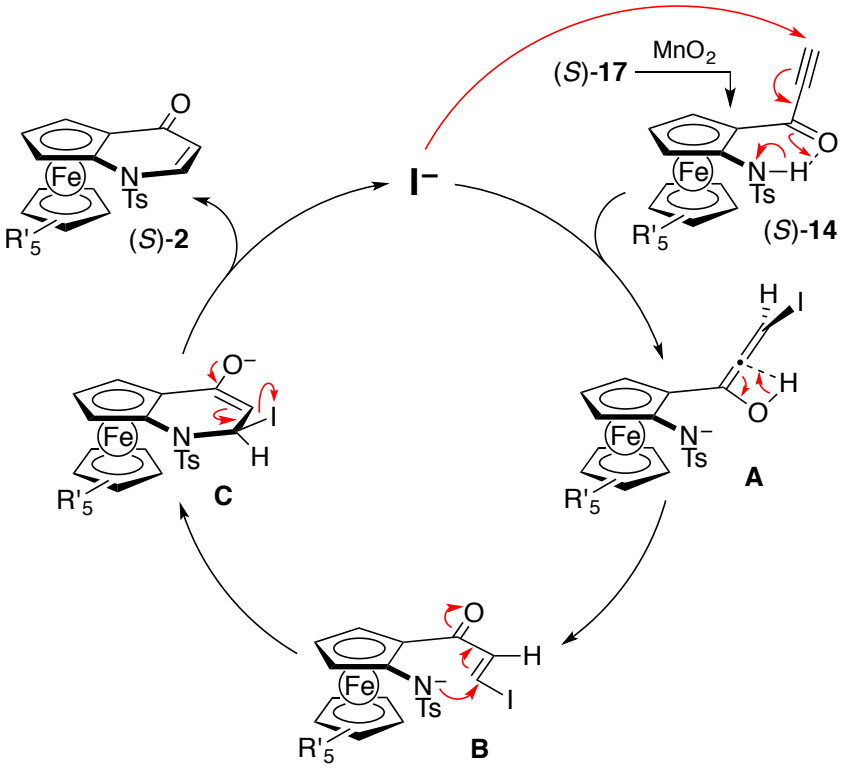


Figure 2. Ball-and-stick drawing of the single-crystal X-ray structure of (*S*)-(–)-**2c** with selected atom numbering.[24]

Scheme 7 shows a plausible reaction mechanism for the iodide-catalyzed cyclization of 1-propynoyl-2-*N*-tosylaminoferrocenes producing the ferrocene-fused *N*-tosyl-4-pyridones. The iodide anion attacks the alkynyl terminal in ynone (*S*)-**14**, which is generated *in situ* by the oxidation of propargylic alcohol (*S*)-**17** with manganese(IV) oxide, to give intermediate **A**. After the isomerization of allenol **A** into enone **B**, the intramolecular conjugate addition of the anionic tosylamide to the enone moiety affords intermediate **C**. Subsequent elimination of the iodide anion from **C** gives pyridone (*S*)-**2** to complete the catalytic cycle. For the effective synthesis of

(*S*)-**2**, the undesirable self-polymerization of (*S*)-**14** should be avoided. Ynone (*S*)-**14**, generated by the oxidation of (*S*)-**17**, needs to react with iodide anion faster than the self-polymerization. This may be a reason why relatively high catalyst-loading (i.e., 50% TBAI) is required to realize the high yields in this process. Although Scheme 7 could explain the formation of (*S*)-**2**, involvement other processes, such as a radical mechanism, could not be ruled out.

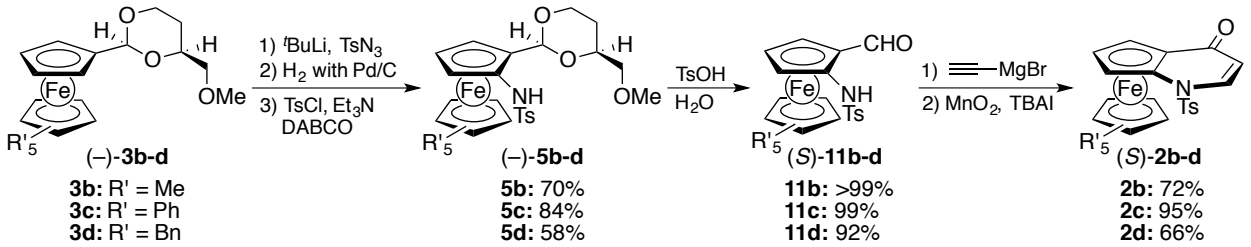


Scheme 7. Plausible Reaction Mechanism for Iodide-Catalyzed Cyclization Producing Ferrocene-Fused 4-Pyridones.

Optimization of Reaction Conditions for More Efficient Synthesis of Planar-Chiral Ferrocene-Fused 4-Pyridones 2. With the iodide-catalyzed cyclization reaction in our hands, the enantioselective synthesis of (*S*)-**2c** was finally accomplished. The synthetic sequence

developed in this study is versatile and applicable to the synthesis of other ferrocene-fused pyridones, such as **2b** and **2d** containing the (η^5-C_5Me_5)Fe and (η^5-C_5Bn_5)Fe moieties, respectively.

To enhance the practicality of this "second-generation synthesis", the reaction conditions for each steps were thoroughly optimized to simplify the synthetic operations. The results are summarized in Scheme 8. The improved enantioselective synthesis of planar-chiral ferrocene-fused pyridones (*S*)-**2** starts from respective chiral acetals (–)-**3** and needs only three isolation/purification steps to (*S*)-**2**. The diastereoselective lithiation of (–)-**3** using ^{t}BuLi followed by a reaction with tosyl azide afforded the corresponding ferrocenyl azide, and the subsequent palladium-catalyzed reduction of the crude azide under a hydrogen atmosphere gave the ferrocenylamine, which was immediately tosylated without purification to provide *N*-tosylaminoferrocenyl acetal (–)-**5** in high yield ranging 58-84%. Acetal (–)-**5**, purified by silica gel column chromatography, was confirmed to be diastereomerically pure by the ^{1}H- and ^{13}C-NMR analyses. The acid-catalyzed hydrolysis of (–)-**5** gave the corresponding aldehyde (*S*)-**11** in >92% yield in enantiomerically pure form. The purification/isolation of (*S*)-**11** may be skipped, but we checked the enantiomeric homogeneity of (*S*)-**11** at this stage. Aldehyde (*S*)-**11** was treated with ethynylmagnesium bromide, and the crude propargylic alcohols, which were obtained by simple extraction, was applied to the iodide-catalyzed cyclization as in Schemes 6/7 to give planar-chiral 4-pyridone (*S*)-**2** in high yield ranging from 66% to 95% (Scheme 8).



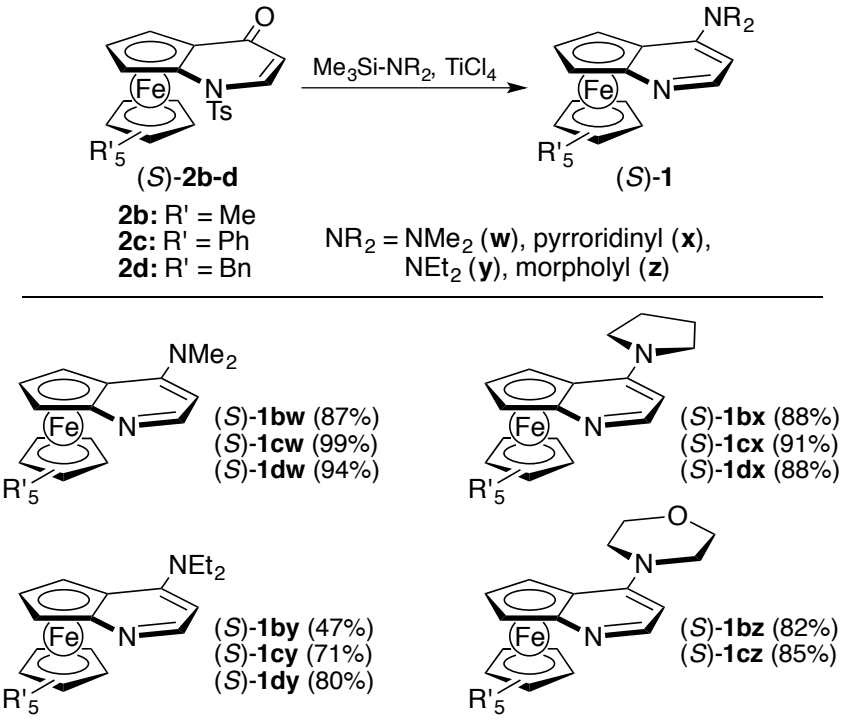
Scheme 8. Optimized Synthetic Sequence for Enantioselective Construction of Ferrocene-Fused 4-Pyridones **2**: "Second-Generation Synthesis" Using Iodide-Catalyzed Cyclization of Propynoyl-*N*-tosylaminoferrocenes.

The second-generation synthesis of pyridones **2** developed here is much shorter with the simpler operations and higher yields compared to the first-generation synthesis. Furthermore, the second-generation synthesis can afford the sterically demanding ferroco-pyridones such as **2c** and **2d**, which are not accessible by the first-generation synthesis. While the total yield from (–)-**3b** to (*S*)-**2b** was 35% in nine-steps by the first-generation synthesis, the second-generation synthesis according to Scheme 8 provided (*S*)-**2b** in 50% total yield starting with (–)-**3b** in six-steps. The synthesis of (*S*)-**2c** was more effective in 71% total yield from (–)-**3c**. The chiral source of the chiral directing group in (–)-**3** is commercially available (*S*)-1,2,4-butanetriol, of which optical antipode, (*R*)-1,2,4-butanetriol, is also commercially available for the synthesis of (*R*)-enantiomers of planar-chiral ferroco-pyridones (*R*)-**3**.

Preparation of Planar-Chiral Ferroco-Pyridines 1 from 4-Pyridones 2. In the previous report, we demonstrated that planar-chiral *N*-tosyl-4-pyridones (*S*)-**2a** and (*S*)-**2b** were versatile precursors to various pyridine derivatives.[13] The direct conversion of (*S*)-**2b** into a series of 4-dialkylaminopyridine derivatives (*S*)-**1bw-bz** was achieved by the reaction with an appropriate *N*-trimethylsilylamine in the presence of titanium(IV) chloride in good to excellent yields (see,

Schemes 2 and 9). This detosylative amination reaction was found to be operative for the sterically demanding ferroco-pyridones such as (*S*)-**2c** and (*S*)-**2d** as well, and the results are summarized in Scheme 9. The reactions introducing dimethylamino, pyrrolidinyl, or morpholyl groups at the 4-position of the pyridine rings proceeded very cleanly and the corresponding Fc-DAAPs were obtained in excellent yields ranging 82-99%. On the other hand, the reaction with diethyl(trimethylsilyl)amine was somewhat slow and the yields of the 4-diethylaminopyridine derivatives are relatively low (47-80%). Steric influence of the η^5-$C_5R'_5$ ligands on the detosylative amination reaction is minimal and three pyridones **2b-d** showed similar reactivity. The isolated yields of the η^5-C_5Me_5 derivatives are somewhat lower, which can be ascribed to their sensitivity toward air-oxidation, since the chromatographic purification was conducted under air.

It should be emphasized that all the transformations shown in Schemes 8 and 9 are stereoretentive. Whereas (*S*)-**2b-d** obtained by our method are enantiomerically pure, planar-chiral ferroco-DAAP derivatives are also single enantiomers. Namely, we have established the divergent process preparing a library of various planar-chiral pyridine-based nucleophilic organocatalysts in enantiomerically pure forms without optical resolution. Our second-generation synthesis is fairly versatile and various substituents can be introduced both at the 4-pyridyl position as well as in the η^5-$C_5R'_5$ moiety. The η^5-pentabenzylcyclopentadienyl derivatives (**1dw-dy**) and 4-diethylamino-/4-morpholyl-ferroco-pyridines (**1by**, **1cy**, **1dy**, **1bz**, and **1cz**) are new compounds and prepared for the first time by our synthetic method.



Scheme 9. Conversion of (*S*)-Ferroco-*N*-tosyl-4-pyridones **2** to Ferroco-DAAP Derivatives **1**.

Single crystals of (*S*)-(–)-**1dw** were grown from pentane/dichloromethane and isolated as deep red prisms. The X-ray crystallography revealed that the compound was single enantiomeric.[24] The absolute configuration of levorotatory **2c** was determined to be (*S*), which is consistent with the stereochemistry deduced from the reported diastereoselective lithiation of the closely related (–)-**3b**.[15,16] All five phenyl groups in the η^5-C_5Bn_5 ligand point away from Fe(1) avoiding the steric interaction with the (η^5-pyrido-Cp)Fe moiety. The ferrocene core in (–)-**3b** shows essentially no distortion with the dihedral angle between the two η^5-ligand being 3.08°.

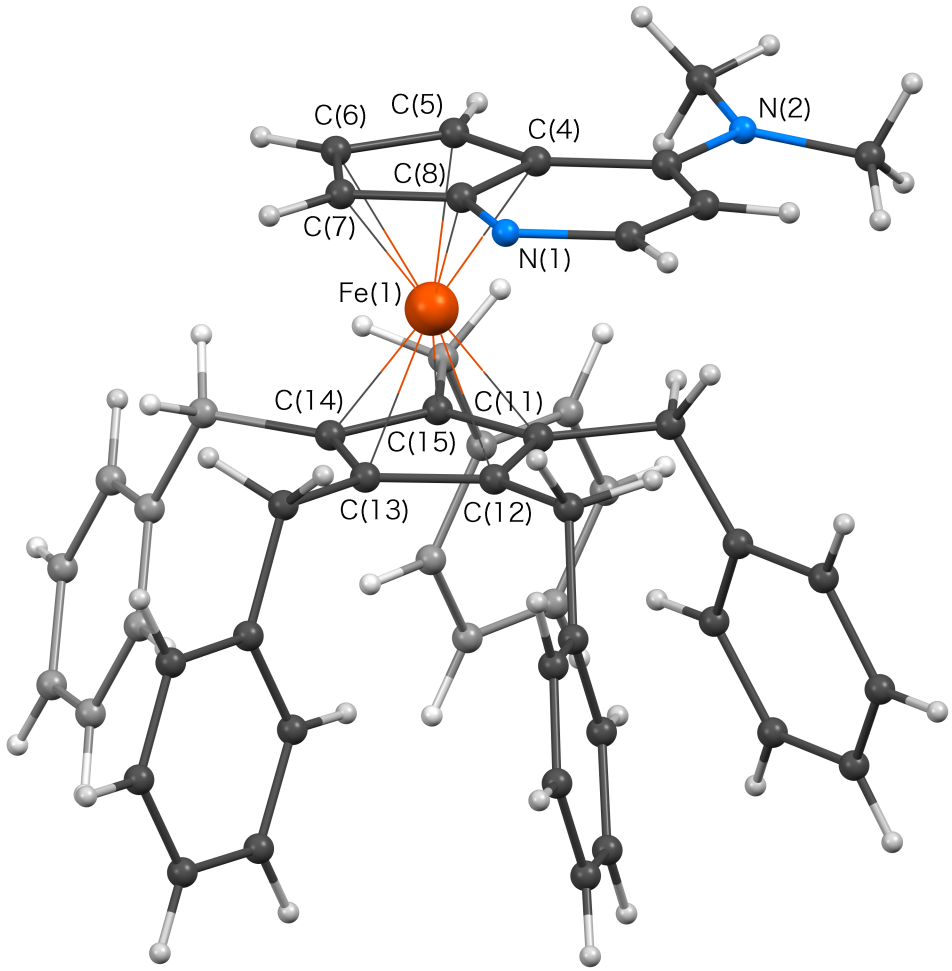
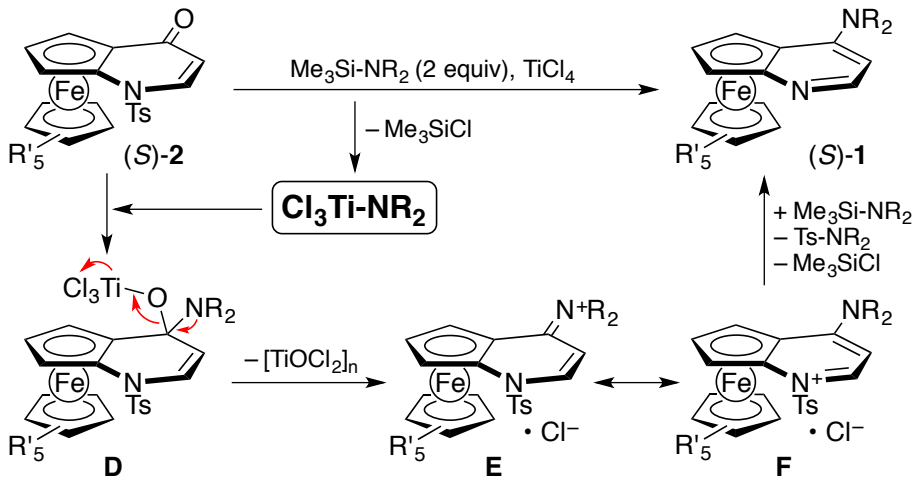


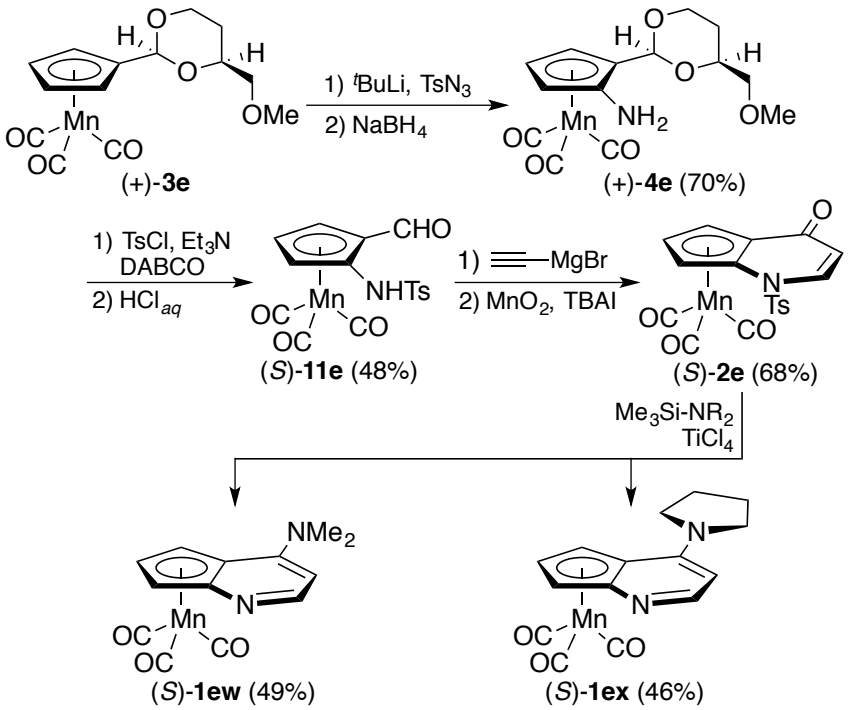
Figure 3. Ball-and-stick drawing of the single-crystal X-ray structure of (*S*)-(–)-**1dw** with selected atom numbering.[24]

A plausible reaction mechanism for the detosylative amination reaction is shown in Scheme 10. A reaction of a trimethylsilylamine with titanium(IV) chloride generates a titanium amide, $Cl_3Ti\text{-}NR_2$, that attacks the carbonyl moiety in (*S*)-**2** to form intermediate **D**. Elimination of titanium(IV) oxodichloride gives iminium species **E**, that also exists in different resonance form **F**. The subsequent reaction of *N*-tosylpyridinium intermediate **F** with $Me_3Si\text{-}NR_2$ affords the corresponding (*S*)-**1** together with tosylamide $TsNR_2$, which was indeed isolated from the reaction mixture.



Scheme 10. Plausible Reaction Pathway of Detosylative Amination of (*S*)-**2** Producing (*S*)-**1**.

Enantioselective Synthesis of Planar-Chiral Cymantrene-Fused DMAP (*S*)-1ew and PPY (*S*)-1ex. The generality of the synthetic method developed in this study was tested on preparation of DAAP derivatives fused with a metallocene other than ferrocenes. Cymantrene, (η^5-cyclopentadienyl)manganese(I) tricarbonyl, was chosen as a platform for this purpose, and the results are shown in Scheme 11. The synthesis began with known chiral cymantrenyl acetal (+)-**3e**,[25] of which sequential diastereoselective lithiation, azidation, and $NaBH_4$ reduction gave aminocymantrene (+)-**4e** in 70% yield as a single-diastereomer. After the *N*-tosylation of (+)-**4e**, the hydrolysis of the chiral acetal moiety using aqueous hydrochloric acid provided aldehyde (*S*)-**11e** in enantiomerically pure form in 48% yield. Treatment of (*S*)-**11e** in the same way as the ferrocene derivatives provided the corresponding cymantrene-fused 4-pyridone (*S*)-**2e** in 68% yield. Pyridone (*S*)-**2e** could be converted to cymantrene-fused DMAP (*S*)-**1ew** and PPY (*S*)-**1ex** in 49% and 46% yields, respectively.



Scheme 11. Enantioselective Synthesis of Planar-Chiral Cymantro-pyridines (*S*)-**1ew** and (*S*)-**1ex**.

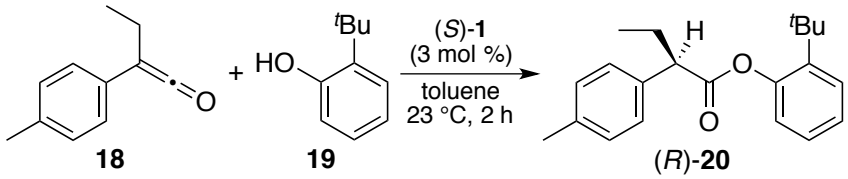
Although the yields of the cymantrene derivatives were lower than those of the ferrocene derivatives, probably due to the air sensitivity of the manganese complexes, the reaction sequence in Scheme 11 demonstrated the versatility and generality of the second-generation synthesis of the planar-chiral DAAP species.

Application of (*S*)-1 in Asymmetric Organocatalysis. The library of the nucleophilic organocatalysts, (*S*)-**1**, obtained in this study was applied in the two prototypical asymmetric reactions and their catalytic performance was evaluated.

The first asymmetric reaction catalyzed by (*S*)-**1** is an addition reaction of 2-*t*Bu-phenol (**19**) to ethyl(*p*-tolyl)ketene (**18**), which was suggested to take place by the Brønsted acid-catalyzed

mechanism (Table 1).[9i] The η^5-C_5Me_5 derivatives, (*S*)-**1bw-bz**, were prepared by our first-generation synthesis and their catalytic applications in this reaction were already examined in the previous report.[13] The reported results are included in the table for comparison (entries 1-4). Among them, ferroco-PPY (*S*)-**1bx**, which is Fu's original, showed good catalytic activity in the addition reaction to give ester **20** in 90% yield with 92% ee (entry 2). The η^5-C_5Ph_5-derivatives, (*S*)-**1cw-cz**, were poor catalysts for this transformation, and **20** was obtained in less than 8% yields with low enantioselectivities of 32% ee at best (entries 5-8). The poor performance of (*S*)-**1cw-cz**, which contain the electron-withdrawing η^5-C_5Ph_5 ligand,[26] could be attributed to their lower basicity compared to (*S*)-**1bw-bz**. And indeed, cymantro-pyridines (*S*)-**1ew-ex**, which were also weakly basic due to the electron-withdrawing nature of the cymantrene framework, showed similar poor catalytic activities and enantioselectivities in the reaction (entries 12-13). On the other hand, η^5-C_5Bn_5-derivatives (*S*)-**1dw-dy**, which contain a bulkier and electron-donating η^5-pentaalkylcyclopentadienide, could be regarded as refined variants of η^5-C_5Me_5-derivatives (*S*)-**1bw-bz** and showed excellent catalytic activities (entries 9-11). Pyridine catalysts (*S*)-**1dw-dy** provided (*R*)-**20** in excellent yields with better enantioselectivities compared to the products obtained by homologous (*S*)-**1bw-by** (entries 5-7 vs entries 9-11). Notably, newly developed (*S*)-**1dx** displayed the highest enantioselectivity of 94% ee in the present reaction and outperformed the other ferroco-/cymantro-pyridines.

Table 1. Enantioselective Addition of *o*-^{t}Bu-Phenol (**19**) to Ethyl(*p*-tolyl)ketene (**18**) Catalyzed by (*S*)-**1**[a]



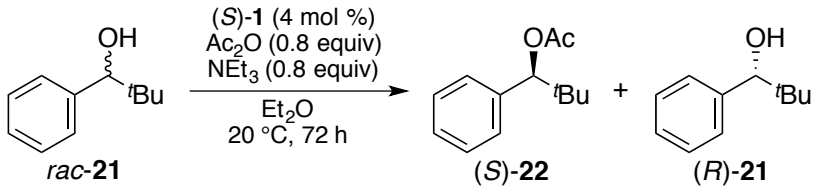
entry	(*S*)-**1**	yield (%)[b]	% ee of **20**[c]
1[d]	**1bw**	92	79
2[d]	**1bx**	90	92
3[d]	**1by**	90	90
4[d]	**1bz**	84	79
5	**1cw**	8	9
6	**1cx**	7	15
7	**1cy**	0	-
8	**1cz**	4	32
9	**1dw**	92	90
10	**1dx**	91	94
11	**1dy**	92	90
12	**1ew**	5	40
13	**1ex**	16	15

[a] The reaction was carried out in toluene at 23 °C in the presence of catalyst (*S*)-**1** (3 mol %). The absolute configuration of **20** was deduced by comparison with the reported results [ref. 9i]. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis on a chiral stationary phase (see the Supporting Information for details). [d] Taken from ref. 13.

The second reaction examined was the kinetic resolution of racemic secondary alcohol *rac*-**21**. The acetylation of *rac*-**21** with acetic anhydride proceeds in an enantioselective fashion in the presence of (*S*)-**1** (4 mol %) to give ester (*S*)-**22** and recovered (*R*)-**21** (Table 2). The catalytic

properties of the η^5-C_5Me_5 derivatives (*S*)-**1bw-bz** were already examined in the previous report[13] and the reported results are included in Table 2 for comparison (entries 1-4). Among the η^5-C_5Me_5 derivatives, (*S*)-**1by** having a 4-diethylamino substituent showed the highest enantioselectivity with *s*-factor[27] of 6.7 (entry 3). It was reported, however, that η^5-C_5Me_5 derivative **1bw** was not an appropriate catalyst for the analogous kinetic resolution of secondary alcohols and the corresponding η^5-C_5Ph_5-derivative **1cw** showed much better enantioselectivity.[9b] With our second-generation synthesis of the planar-chiral DAAPs, a series of η^5-C_5Ph_5-derivatives (*S*)-**1cw-cz** were available for this study. As we expected, indeed, (*S*)-**1cw-cz** showed excellent enantioselectivities with *s*-factors ranging 13 to 69 (entries 5-8). The best selectivity (*s* = 69) was recorded using (*S*)-**1cz**, which was prepared for the first time in this study, but its catalytic activity was decreased due to the less electron-donating ability of the 4-morpholyl substituent (entry 8). The performance of η^5-C_5Bn_5 derivatives (*S*)-**1dw-dy** was somewhat similar to that of (*S*)-**1bw-by**, but the former showed slightly better selectivities than the latter (entries 9-11). Once again, (*S*)-**1dw-dy** can be seen as improved variants of (*S*)-**1bw-by**. Cymantrene-fused DMAP (*S*)-**1ew** and PPY (*S*)-**1ex** were also applied to the kinetic resolution of *rac*-**21**. The results were, however, unsatisfactory in terms of both catalytic activity and enantioselectivity, which can be ascribed to the less electron-donating and the sterically compact character of the cymantrene platform in (*S*)-**1ew-ex** (entries 12 and 13).

Table 2. Enantioselective Acetylation of *rac*-**21** Catalyzed by (*S*)-**1**[a]



entry	(*S*)-**1**	conv (%)[b]	% ee of **22**[c]	% ee of **21**[c]	*s*-factor[d]
1[e]	**1bw**	65	41	75	5.0
2[e]	**1bx**	62	43	70	5.0
3[e]	**1by**	70	39	92	6.7
4[e]	**1bz**	66	41	78	5.3
5	**1cw**	41	89	62	33
6	**1cx**	46	91	76	48
7	**1cy**	45	75	60	13
8	**1cz**	7	97	8	69
9	**1dw**	62	47	78	6.3
10	**1dx**	66	43	83	6.0
11	**1dy**	68	45	98	11
12	**1ew**	31	50	23	3.7
13	**1ex**	27	54	19	4.0

[a] The reaction was carried out in diethyl 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 **22** and recovered **21** were determined by comparison with the reported results [ref. 9b]. [d] Calculated based on a first-order equation [ref. 27]. [e] Taken from ref. 13.

Conclusions

In summary, we have developed a substantially improved method of preparing various metallocene-fused planar-chiral 4-pyridones **2**/4-dialkylaminopyridines **1** in enantiomerically pure forms. The renewed method, "second-generation synthesis of Fc-DAAPs", is much more practical and advantageous than our previous enantioselective synthesis of **2**/**1**, because it is (i) with shorter and more efficient synthetic sequence, (ii) results in higher yields of **2**/**1**, (iii) no need for expensive noble metal catalysts, and (iv) accessible to sterically demanding Fc-DAAPs having an (η^5-C_5Ph_5)Fe or (η^5-C_5Bn_5)Fe moiety. Whereas the bulky Fc-DAAP derivatives are synthetically more useful showing better enantioselectivity in general, the last point is particularly important innovation in the present protocol. These bulky Fc-DAAPs could not be prepared by our first-generation synthesis. The η^5-C_5Bn_5-DAAP derivatives are previously unknown and prepared for the first time in the present studies. The success of the second-generation synthesis depends in large part on the discovery of the iodide-catalyzed cyclization of 1-propynoyl-2-*N*-tosylaminoferrocenes **14** giving the corresponding 4-pyridones **2** in excellent yields. One unique feature of our synthesis of Fc-DAAPs is the late stage introduction of various dialkylamino-substituents at the 4-position of Fc-DAAPs by the detosylative amination of **2**. Since the detosylative amination worked efficiently even on the bulky pyridones such as **2c** and **2d**, our method is divergent and could provide a library of planar-chiral pyridine-based nucleophilic organocatalysts. Due to the versatility of the second-generation synthesis, a new family of planar-chiral DAAP derivatives, cymantrene-fused DAAPs **1e**, were also prepared in the same way.

Finally, the library of the planar-chiral DAAPs were examined in the two prototypical asymmetric reactions as organocatalysts. Some newly prepared Fc-DAAP derivatives showed

better performance than the known species in these reactions. This is a clear-cut advantage of having the library of Fc-DAAPs.

Since the development of Fc-DAAPs **1** in 1990s by Fu, these compounds have been recognized as one of the most attractive and versatile chiral nucleophilic catalysts showing applicability to a wide range of asymmetric reactions. We believe that present study should contribute further development of these unique molecules.

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ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: *********.

The following files are available free of charge.

Experimental procedures and compound characterization data (PDF)

Crystallographic data for (*S*)-(–)-**2c** and (*S*)-(–)-**1dw** (CIF)

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