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Enantioselective Rh-Catalyzed Hydrogenation of 3-Aryl-2-phosphonomethylpropenoates by a New Class of Chiral Ferrocenyl Diphosphine Ligands

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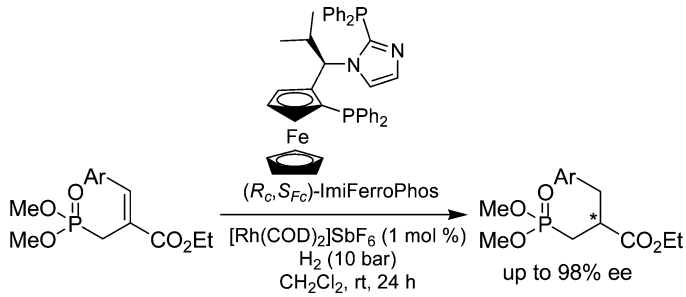
ABSTRACT



A new class of chiral ferrocenyl diphosphine ligands with an imidazole ring, (R_c,S_{Fc})-ImiFerroPhos, has been prepared from acylferrocenes through a five-step transformation and successfully applied in the Rh-catalyzed asymmetric hydrogenation of various 3-aryl-substituted 2-phosphonomethylpropenoates, in which a series of chiral 3-phosphono-2-arylmethylpropanoic acid derivatives were achieved in ee values of up to 98%.

Chiral 3-phosphono-2-alkylpropanoic acid derivatives have received considerable attention in the past few years in bioorganic and medicinal chemistry because of their important biological activities as phosphonate and phosphinate enzyme inhibitors.[1] The present syntheses of enantioenriched 3-phosphono-2-alkylpropanoic acid derivatives mainly focused on the asymmetric induction using a chiral auxiliary.[2] However, not only are these methods not catalytic, requiring stoichiometric chiral materials, but also in many cases the diastereoselectivity obtained is unsatisfactory. The need for the development of an efficient and catalytic method for enantioselective synthesis of chiral 3-phosphono-2-alkylpropanoic acid derivatives is therefore apparent. Very recently, Spilling et al. have described an example of enantioselective synthesis of chiral 3-phosphono-2-alkylpropanoic acids or esters by a catalytic asymmetric hydrogenation of the corresponding 2-phosphonomethylpropenoate derivatives.[3] Given its inherent efficiency and atom economy, the catalytic asymmetric hydrogenation[4] would seem to be an ideal approach to prepare enantiopure chiral 3-phosphono-2-alkylpropanoic acid derivatives. However, the research disclosed that the level of asymmetric induction with Rh/diphosphine (e.g., DIPAMP, DuPHOS, ferrotane, Tangphos)[3] complexes was very low (0−52% ee). Although an improved

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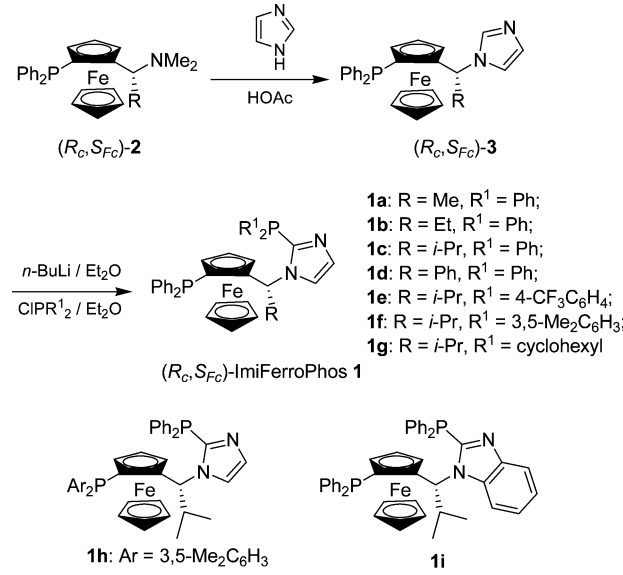
enantioselectivity (up to 91% ee) was observed in the hydrogenation of 2-phosphonomethylpropenoic acids with a (*R*)-Cl-MeO-BIPHEP-Ru catalyst,[3] for most substrates, the enantioselectivities were still less satifactory. Therefore, the search of a new catalytic system for the enantioselective hydrogenation of a wider range of 2-phosphonomethylpropenoate derivatives is still highly desirable. As a part of our ongoing efforts in the development of new catalytic hydrogenation methods for the enantioselective synthesis of chiral phosphonates,[5] herein we report a highly enantioselective synthesis of chiral 3-phosphono-2-arylmethylpropanoic acid esters via the rhodium-catalyzed asymmetric hydrogenation with a new class of chiral diphosphine ligands [(R_c,S_{Fc})-ImiFerroPhos] based on ferrocenyl and heterocyclic scaffolds.

In the past few years, many ferrocenyl diphosphine ligands with subtle structural variations have been developed and successfully employed in a variety of asymmetric catalyses.[6] However, ferrocenyl bisphosphine ligands with a heterocycle remain less explored.[7] These ligands are more amenable to asymmetric catalysis than many other types of chiral ligands as a result of their easy accessibility and derivatization as well as special electronic and steric properties. Indeed, new chiral ImiFerroPhos ligands, with an imidazole ring, can be easily prepared from acylferrocenes through a modular procedure, and they display superior enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of this challenging substrate class.

The synthetic route for (R_c,S_{Fc})-ImiFerroPhos **1a**−**i** is illustrated in Scheme 1.

Scheme 1. Preparation of (R_c,S_{Fc})-ImiFerroPhos **1a**−**i**



The chiral ferrocene-based phosphine−amine compounds (R_c,S_{Fc})-PPFA-R **2** were used as the starting materials, which can be readily prepared from acylferrocenes through a three-step transformation according to the literature procedure.[8] Heating (R_c,S_{Fc})-**2** with imidazole in AcOH afforded (R_c,S_{Fc})-**3** with complete configurational retention at the central chirality.[9] The treatment of (R_c,S_{Fc})-**3** with 1.5 molar equiv of *n*-BuLi in Et_2O at rt or −78 °C followed by trapping with 1.5 molar equiv of $ClPR^1_2$ gave the target diphosphine ligands (R_c,S_{Fc})-ImiFerroPhos **1a**−**g** in moderate yields. In a similar synthetic procedure, ligands (R_c,S_{Fc})-**1h**−**i** were prepared from the corresponding phosphine−amine intermediates in moderate yields. (R_c,S_{Fc})-ImiFerroPhos **1a**−**i** are air-stable and can be handled in air, which makes the synthesis, use, and storage of these ligands very convenient.

The structure of (R_c,S_{Fc})-ImiFerroPhos **1c** was confirmed by X-ray crystallography (Figure 1).

With these newly developed diphosphine ligands in hand, we then examined their efficiency in the Rh-catalyzed asymmetric hydrogenation of this challenging substrate class, 2-phosphonomethylpropenoates **4**.[10] Initially, ethyl 2-

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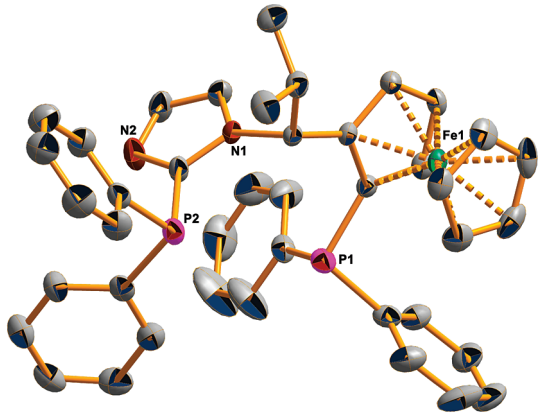
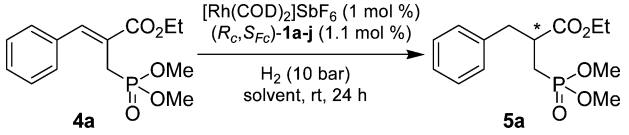


Figure 1. Crystal structure of (R_c,S_{Fc})-ImiFerroPhos **1c**. The hydrogen atoms and solvent were omitted for clarity.

[(dimethoxyphosphoryl)methyl]-3-phenyl-2-propenoate **4a** was used as a model substrate for ligand screening and condition optimizing experiments. All reactions were carried out at room temperature under 10 bar of H_2 pressure for 24 h and with an Rh:ligand ratio of 1:1.1, and the results are summarized in Table 1. With (R_c,S_{Fc})-ImiFerroPhos **1a** having a methyl substituent in the ferrocenylmethyl position, **4a** was hydrogenated to **5a** in 76% ee (entry 1). Introducing an ethyl group [(R_c,S_{Fc})-ImiFerroPhos **1b**] increased the enantioselectivity to 88% ee (entry 2). The enantioselectivity was further increased to 94% ee with (R_c,S_{Fc})-ImiFerroPhos **1c** bearing an *i*-Pr group (entry 3). However, a phenyl group in the ferrocenylmethyl position [(R_c,S_{Fc})-ImiFerroPhos **1d**] resulted in a decrease of enantioselectivity to 78% ee (entry 4). Comparison of the results obtained with (R_c,S_{Fc})-ImiFerroPhos **1a**−**d** suggested that the steric demand in the ferrocenylmethyl position of these newly developed ligands is crucial for achieving high enantioselectivity in the hydrogenation of this challenging substrate class. Phosphino groups in these ligands have also greatly affected the reactivities and enantioselectivities. However, no ligand showed superior enantioselectivity to that obtained with (R_c,S_{Fc})-ImiFerroPhos **1c** (entries 5−9). It is noteworthy that both the catalytic activity and enantioselectivity of the Rh/(R_c,S_{Fc})-ImiFerroPhos **1c** complex are sensitive to the solvent used. The protonic solvents such as MeOH and *i*-PrOH tended to give lower conversions and enantioselectivities (entries 10−11). The reaction proceeded smoothly in THF, giving slightly lower enantioselectivity (entry 12). Toluene proved to be an inferior solvent, in which low conversion was observed (entry 13). Lowering the catalyst loading to 0.1 mol % resulted in the dramatically decreased conversion (entry 14).

Having established the optimal ligand and solvent, we next investigated the effect of the ester functional group of 2-phosphonomethylpropenoates on this hydrogenation. The results are summarized in Table 2. Initially, the hydrogenation of 2-[(dimethoxyphosphoryl)methyl]-3-phenyl-2-propenoates **4a**−**c** with the different ester functional group in the carboxylic moiety was examined (entries 1−3). It is very strange that a modest change from an ethyl ester (**4a**) to a

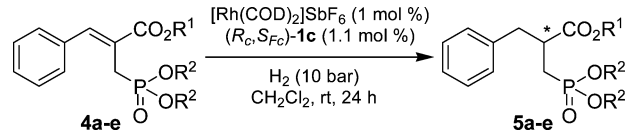
Table 1. Rh-Catalyzed Asymmetric Hydrogenation of Ethyl 2-[(Dimethoxyphosphoryl)methyl]-3-phenyl-2-propenoate **4a** with (R_c,S_{Fc})-ImiFerroPhos **1a**−**j** as Ligands[a]



entry	ligand	solvent	convn (%)[b]	ee (%)[c]
1	(R_c,S_{Fc})-**1a**	CH_2Cl_2	>95	76
2	(R_c,S_{Fc})-**1b**	CH_2Cl_2	>95	88
3	(R_c,S_{Fc})-**1c**	CH_2Cl_2	>95	94
4	(R_c,S_{Fc})-**1d**	CH_2Cl_2	>95	78
5	(R_c,S_{Fc})-**1e**	CH_2Cl_2	>95	86
6	(R_c,S_{Fc})-**1f**	CH_2Cl_2	>95	88
7	(R_c,S_{Fc})-**1g**	CH_2Cl_2	>95	52
8	(R_c,S_{Fc})-**1h**	CH_2Cl_2	91	94
9	(R_c,S_{Fc})-**1i**	CH_2Cl_2	>95	91
10	(R_c,S_{Fc})-**1c**	MeOH	81	83
11	(R_c,S_{Fc})-**1c**	*i*-PrOH	92	80
12	(R_c,S_{Fc})-**1c**	THF	>95	90
13	(R_c,S_{Fc})-**1c**	toluene	56	77
14	(R_c,S_{Fc})-**1c**	CH_2Cl_2	<10	–[d]

[a] Reactions conditions: 2 mL of solvent, 0.5 mmol of substrate **4a**, 1 mol % of catalyst prepared in situ from $[Rh(COD)_2]SbF_6$ and 1.1 equiv of (R_c,S_{Fc})-ImiFerroPhos **1a**−**i**, 10 bar of H_2 pressure, room temperature for 24 h. [b] Conversions were determined by ^1H NMR. [c] Enantiomeric excesses were determined by HPLC, using a chiralcel OD-H column. [d] Using 0.1 mol % of [Rh].

Table 2. Effect of Ester Functional Group in the Rh-Catalyzed Hydrogenation of 2-Phosphonomethylpropenoates with (R_c,S_{Fc})-ImiFerroPhos **1c** as Ligand[a]



entry	substrate	R^1	R^2	convn (%)[b]	ee (%)[c]
1	**4a**	Et	Me	>95	94
2	**4b**	Me	Me	29	–[d]
3	**4c**	*t*-Bu	Me	79	88
4	**4d**	Et	*i*-Pr	81	94
5	**4e**	Et	Ph	>95	82

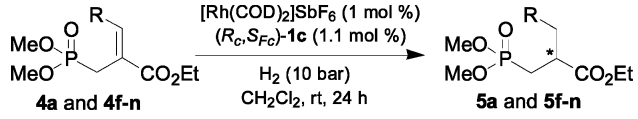
[a] Reactions conditions: 2 mL of CH_2Cl_2, 0.5 mmol of substrate, 1 mol % of catalyst prepared in situ from $[Rh(COD)_2]SbF_6$ and 1.1 equiv of (R_c,S_{Fc})-ImiFerroPhos **1c**, 10 bar of H_2 pressure, room temperature for 24 h. [b] Conversions were determined by ^1H NMR. [c] Enantiomeric excesses were determined by HPLC, using a chiralcel OD-H column. [d] Not determined because of low conversion.

(10) The substrates **4a**−**n**, prepared by the reaction of the Baylis−Hillman adducts with phosphorchloridite in the presence of triethylamine, have exclusively the *Z*-configuration. For the literature, see: Janecki, T.; Bodalski, R. *Synthesis* **1990**, 799.

methyl ester (**4b**) led to the dramatically decreased conversion (entry 1 vs entry 2). The hydrogenation of the substrate **4c** with a bulky *t*-Bu ester function also resulted in the reduced conversion and enantioselectivity (entry 3). The introduction of the bulkier ester functional group into the phosphoryl moiety did not affect the enantioselectivity but lowered the conversion to 81% (entry 4). On the contrary, the substrate with a phenyl ester functional group in the phosphoryl moiety gave full conversions and decreased enantioselectivity (entry 5). These results suggested that the ester functional group of 2-phosphonomethylpropenoates has a significant influence on the conversion and enantioselectivity.

Encouraged by these results, we then examined the Rh-catalyzed asymmetric hydrogenation of a variety of ethyl 3-aryl-2-[(dimethoxyphosphoryl)methyl]-2-propenoates **4f**−**m** with (R_c,S_{Fc})-ImiFerroPhos **1c** under the optimized conditions (Table 3). In all cases, full conversions and high yields were achieved. The electronic nature of the *para*-substituents on the phenyl ring has some effect on the enantioselectivity (entries 2−5). The substrate with an electron-donating group tended to give higher enantioselectivity than those with electron-withdrawing substituents. Thus, the substrate **4h** with an NO_2 group was hydrogenated with 89% ee, while the hydrogenation of a methoxy-substituted substrate **4i** gave the hydrogenation product in 95% ee (entry 4 vs entry 5). It appears that the position of the substituent on the phenyl ring had a limited effect on the enantioselectivities. All of the substrates with a methoxy group in the different position of the phenyl ring were hydrogenated with similar enantioselectivities (entries 5−7). The hydrogenation of the substrates with a heteroaromatic substituent also led to good enantioselectivities. Remarkably, the hydrogenation of 2-thienyl-substituted substrate **4m** provided the best enantioselectivity of up to 98% ee (entry 9). These results demonstrate the high efficiency of the present catalytic system in the Rh-catalyzed asymmetric hydrogenation of this challenging substrate class. However, this catalytic system is inefficient for the hydrogenation of alkyl-substituted substrate **4n** (entry 10).

Table 3. Rh-Catalyzed Hydrogenation of Ethyl 2-[(Dimethoxyphosphoryl)methyl]-3-aryl-2-propenoate **4f**−**n** with (R_c,S_{Fc})-ImiFerroPhos **1c** as Ligand[a]



entry	substrate	R	convn (%)[b]	yield (%)[c]	ee (%)[d]
1	**4a**	Ph	>95	98	94
2	**4f**	4-FC_6H_4	>95	94	91
3	**4g**	4-ClC_6H_4	>95	98	92
4	**4h**	4-$NO_2C_6H_4$	>95	91	89
5	**4i**	4-$MeOC_6H_4$	>95	98	95
6	**4j**	3-$MeOC_6H_4$	>95	98	92
7	**4k**	2-$MeOC_6H_4$	>95	99	93
8	**4l**	2-furyl	>95	97	90
9	**4m**	2-thienyl	>95	98	98
10	**4n**	*i*-Pr	<5	–	–[e]

[a] Reactions conditions: 2 mL of CH_2Cl_2, 0.5 mmol of substrate, 1 mol % of catalyst prepared in situ from $[Rh(COD)_2]SbF_6$ and 1.1 equiv of (R_c,S_{Fc})-ImiFerroPhos **1c**, 10 bar of H_2 pressure, room temperature for 24 h. [b] Conversions were determined by ^1H NMR. [c] Isolated yields. [d] Enantiomeric excesses were determined by HPLC, using a chiral AD-H, OD-H, or OJ-H column. [e] Not determined because of low conversion.

In conclusion, we have developed a new family of chiral ferrocenyl diphosphine ligands with an imidazole ring, (R_c,S_{Fc})-ImiFerroPhos **1a**−**i**, through a five-step procedure from acylferrocenes. The modular construction of this ligand class allows for wide structural diversity. These ligands have been successfully applied in the Rh-catalyzed asymmetric hydrogenation of a challenging substrate class, 2-phosphonomethylpropenoates, giving the best results reported so far. The further applications of this new ligand class in asymmetric catalysis will be disclosed in due time.

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Supporting Information Available: Experimental details, optimization data, spectra for new compounds, and analysis of ee value of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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