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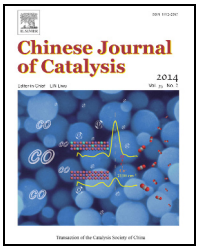

Article

Rh-ImiFerroPhos complexes catalyzed asymmetric hydrogenation of β-substituted α,β-unsaturated phosphonates

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ABSTRACT

A series of chiral ferrocenyl diphosphine ligands (ImiFerroPhos ligands) has been applied to the hydrogenation of β-substituted α,β-unsaturated phosphonates to generate a range of optically active β-substituted alkylphosphonates in good yields with good enantioselectivity (up to 92% ee) under mild reaction conditions.

1. Introduction

It is envisaged that chiral phosphonates will become increasingly useful chiral building blocks in organic synthesis [1–8]. Furthermore, there has been considerable interest in the biological properties of the phosphorus analogues of carboxylic acids [9,10]. Although several efficient processes have been developed during the past few decades for synthesis of chiral 1-arylethylphosphonates [11–18], methods for the catalytic enantioselective synthesis of chiral alkylphosphonates, especially those bearing a β-stereogenic center, remain scarce [19–21]. Given its inherent efficiency and atom economy, it was envisaged that catalytic asymmetric hydrogenation [22–29] would provide an ideal approach for the preparation of chiral phosphonate derivatives. We recently developed several new synthetic methods involving the Rh-catalyzed asymmetric hydrogenation of β-substituted α,β-unsaturated phosphonates [30,31] and β-substituted β,γ-unsaturated phosphonates [32,33]. Although there have already been several reports in the literature pertaining to the asymmetric hydrogenation of unsaturated phosphonates, the number of effective catalysts available for this transformation is limited, and the research towards the development of new catalysts remains a great challenge.

In our previous study, we developed a series of chiral ImiFerroPhos ligands and used the rhodium complexes of the ligand to affect the highly enantioselective hydrogenation of a series of 3-aryl-substituted 2-phosphonomethylpropenoates [34]. The structure of the ImiFerroPhos ligands was similar to that of the TaniaPhos ligand, which showed high levels of activity towards the hydrogenation of β-substituted α,β-unsaturated phosphonates but provided poor enantioselectivity. The

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ImiFerroPhos ligands, which contain a heterocycle, are more amenable to asymmetric catalysis than other chiral ligands because they can be readily constructed and derivatized, and possess unique electronic and steric properties. In the current study, we investigated the application of ImiFerroPhos ligands to the Rh-catalyzed asymmetric hydrogenation of β-substituted α,β-unsaturated phosphonates. The ImiFerroPhos ligands performed effectively in this regard to give the corresponding chiral phosphonates in good to high enantioselectivity under mild hydrogenation condition.

2. Experimental

2.1. General methods

All of the reactions and manipulations were performed in a nitrogen-filled glove box or under a nitrogen atmosphere using Schlenk techniques unless otherwise noted. All of the solvents were distilled under argon in the presence of the following desiccants: sodium and benzophenone for toluene and tetrahydrofuran (THF), and CaH_2 for dichloromethane (CH_2Cl_2). The NMR spectra were obtained on a Bruker DRX 400 spectrometer. ^{31}P NMR shifts were referenced to external 85% H_3PO_4, while ^{13}C and ^{1}H NMR shifts were referenced to the residual signals of deuterated solvents.

2.2. Preparation of ligands

All of the ligands used in the current study were prepared according to previously reported procedures [34].

1-{(*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]lpropyl}-2-(diphenylphosphino)benzimidazole (**Le**). Orange crystals; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.63 (t, J = 8.0 Hz, 3H), 2.35 (m, 1H), 2.54 (m, 1H), 3.87 (s, 1H), 4.07 (m, 4H), 4.12 (s, 1H), 4.43 (s, 1H), 4.90 (s, 1H), 5.82 (m, 2H), 6.39 (m, 2H), 6.70 (m, 1H), 6.87 (m, 1H), 7.04 (m, 2H), 7.25 (m, 8H), 7.32 (m, 3H), 7.43 (m, 2H), 7.65 (m, 2H), 7.75 (m, 2H); ^{13}C NMR (100 MHz $CDCl_3$): δ 11.3, 28.9, 60.8 (d, J = 20 Hz), 68.3, 69.4, 70.1, 71.5, 74.4, 91.9, 111.7, 118.6, 120.0, 120.8, 125.3, 125.6, 126.2, 126.9, 127.0, 127.7, 128.2, 129.8, 133.1, 134.6, 135.6, 136.3, 136.8, 137.8; ^{31}P NMR (162 MHz, $CDCl_3$): δ –25.5 (d, J = 59.9 Hz), –34.5 (d, J = 55.1 Hz); HRMS (ESI): calcd for $C_{44}H_{38}FeN_2P_2$ $[M+H]^+$, 713.1938; found, 713.1922.

2.3. General procedure for the preparation of β-substituted α,β-unsaturated phosphonates

A solution of $(EtO)_2P(O)CH_2P(O)(OEt)_2$ (1.44 g, 5 mmol) in THF (2 ml) was slowly added to a slurry of NaH (0.19 g, 5.5 mmol, 70% in oil) in THF (10 ml) at 0 °C, and the resulting mixture was stirred at room temperature for 30 min. A solution of ketone (4.25 mmol) in THF (3 ml) was then added to the reaction, and the resulting mixture was stirred at room temperature until the ketone could no longer be detected by TLC. The mixture was then diluted with ether and washed sequentially with an aqueous solution of saturated NH_4Cl (25 ml) and brine (25 ml) before being dried over anhydrous Na_2SO_4 and distilled to dryness in vacuo to give the crude product as a residue, which was purified by column chromatography (silica gel, EtOAc:hexane = 1:1).

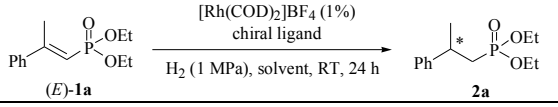
2.4. General procedure for asymmetric hydrogenation of α,β-unsaturated phosphonates

In a nitrogen-filled glove box, $[Rh(COD)_2]BF_4$ (1.0 mg, 0.0025 mmol) and (R_c,S_{Fc})-ImiFerroPhos (0.0028 mmol) were dissolved in degassed CH_2Cl_2 (1 ml) in a 5 ml vial. Following a 15-min period of stirring at room temperature, a solution of α,β-unsaturated phosphonate (**1,** 0.25 mmol, S/C = 100) in degassed CH_2Cl_2 (1 ml) was added to the reaction vial, and the resulting mixture was transferred to an autoclave. The autoclave was then charged with H_2 (≈ 1 MPa), and the reaction mixture was hydrogenated at room temperature for 24 h. The H_2 gas was carefully released from the autoclave, and the reaction mixture was passed through a plug of silica gel (eluting with a mixture of hexanes/EtOAc) to afford β-substituted alkylphosphonates (**2**). The enantiomeric excess was determined by HPLC on a chiral stationary phase.

3. Results and discussion

Diethyl (*E*)-(2-phenyl-1-propene) phosphonate (*E*)**-1a** was initially selected as a model substrate for the ligand screening and optimization experiments for the Rh-catalyzed asymmetric hydrogenation reaction. The reactions were typically conducted at room temperature for 24 h in CH_2Cl_2 under 1 MPa of H_2 pressure using 1% of $[Rh(COD)_2]BF_4$ and 1.1% of ligand. The results are summarized in Table 1. When (R_c,S_{Fc})-ImiFerroPhos **La** (Fig. 1) bearing a methyl substituent in the ferrocenylmethyl position was used as the ligand, **1a** was hydrogenated to give **2a** in 82% ee (Table 1, entry 2). This result showed that ImiFerroPhos, which contained a heterocycle, was more efficient than TaniaPhos (Table 1, entry 2 vs entry 1). The intro-

Table 1
Asymmetric hydrogenation of diethyl (*E*)-(2-phenyl-1-propenyl) phosphonate (**1a**).



(*E*)-**1a** **2a**

Entry	Ligand	Solvent	Conversion[a] (%)	ee[b] (%)
1	TaniaPhos	CH_2Cl_2	100	54 (*R*)
2	**La**	CH_2Cl_2	100	82 (*S*)
3	**Lb**	CH_2Cl_2	100	83 (*S*)
4	**Lc**	CH_2Cl_2	100	81 (*S*)
5	**Ld**	CH_2Cl_2	100	75 (*S*)
6	**Le**	CH_2Cl_2	100	90 (*S*)
7	**Le**	MeOH	45	—[c]
8	**Le**	*i*-PrOH	100	89 (*S*)
9	**Le**	THF	61	77 (*S*)
10	**Le**	Toluene	5	—[c]

The reactions were carried out with 0.25 mmol of substrate at room temperature under H_2 pressure of 1 MPa in 2 ml of the indicated solvent for 24 h.

[a] Determined by GC.

[b] Determined by HPLC on a chiral column.

[c] Not determined because of low conversion.

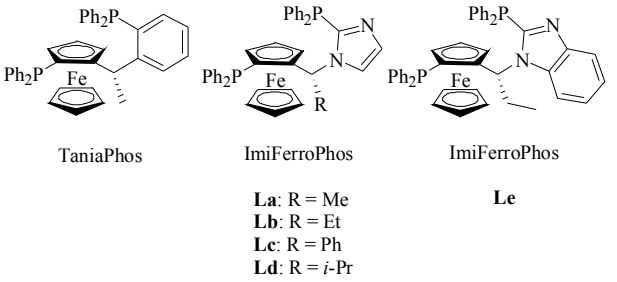


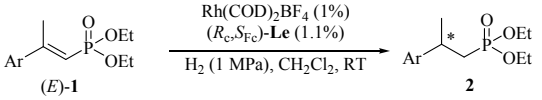
Fig. 1. Structure of the ligands used for the asymmetric hydrogenation.

duction of an ethyl group, as in (R_c,S_{Fc})-ImiFerroPhos **Lb**, increased the enantioselectivity of the transformation very slightly to 83% ee (Table 1, entry 3). Further increases in the size of the substituent at the ferrocenyl position to a phenyl (**Lc**) or *i*-Pr (**Ld**) group, however, resulted in a reduction in the enantioselectivity to 81% and 75% ee (Table 1, entries 4 and 5), respectively. The conversion of the imidazole heterocycle in **Lb** to a benzimidazole (ligand **Le**) led to an increase in the ee value to 90% (Table 1, entry 6).

It is noteworthy that both the catalytic activity and enantioselectivity of the Rh/(R_c,S_{Fc})-ImiFerroPhos **Le** complex were sensitive to the solvent used. The use of protonic solvents such as MeOH and *i*-PrOH provided mixed results. For example, the MeOH provided a much lower conversion (Table 1, entry 7), whereas the *i*-PrOH gave complete conversion, albeit with a slightly lower enantioselectivity (Table 1, entry 8). THF and toluene proved to be inferior solvents and gave lower conversions, with toluene providing the lowest conversion of all of the solvents tested in the current study (Table 1, entries 9 and 10).

Encouraged by the positive results obtained for the hydrogenation of (*E*)-**1a**, we proceeded to investigate the scope of this transformation towards a variety of different β-substituted α,β-unsaturated phosphonates **1a**–**1k**, using (R_c,S_{Fc})-ImiFerroPhos **Le** as the ligand and CH_2Cl_2 as the solvent under H_2 pressure of 1 MPa at room temperature for 24 h. As shown in Table 2, a range of β-aryl-α,β-unsaturated phosphonates (*E*)-**1a**–**1h** were successfully hydrogenated under the optimized conditions to give the corresponding 2-arylpropylphosphonates in good yields and good to high enantioselectivity (up to 92% ee). These results indicated that the current catalytic system was tolerant to the electronic properties of the substituents on the phenyl ring of the substrate in terms of the impact of these properties on the reactivity and enantioselectivity of the transformation. The position of the substituent on the phenyl ring appeared to have very little impact on the outcome of the reaction. Three substrates bearing a methoxy group at the *ortho*, *meta*, or *para* position of the phenyl ring were hydrogenated in good enantioselectivity (Table 2, entries 2–4). The electronic properties of the substituents at the *para* position of the phenyl ring also appeared to have very little impact on the enantioselectivity, with electron withdrawing and electron donating groups at this position providing similar results. Diethyl (*E*)-[2-(2-naphthyl)-1-propenyl] phosphonate (**1g**) and the (*S*)-heteroaromatic substrate **1h** were also successfully hydrogenated under the optimized conditions to give the desired products in 84% and 86% ee, respectively (Table 2, entries 7 and 8).

Table 2
Asymmetric hydrogenation of diethyl (*E*)-(2-aryl-1-propene) phosphonates (**1a**–**1h**).



Entry	Substrate	Ar	Yield [a] (%)	ee [b] (%)
1	**1a**	Ph	98	90 (*S*)
2	**1b**	2-MeOC$_6$H$_4$	94	90 (–)
3	**1c**	3-MeOC$_6$H$_4$	95	90 (–)
4	**1d**	4-MeOC$_6$H$_4$	96	86 (–)
5	**1e**	4-FC$_6$H$_4$	97	92 (–)
6	**1f**	4-ClC$_6$H$_4$	96	91 (–)
7	**1g**	2-naphthyl	94	84 (–)
8	**1h**	2-thiophenyl	95	86 (–)

All reactions were carried out with 0.25 mmol of substrate at room temperature under H_2 pressure of 1 MPa in 2 ml of CH_2Cl_2 for 24 h with substrate:Rh(COD)$_2$BF$_4$:ligand = 1:0.01:0.011.

[a] Isolated yield.

[b] Determined by HPLC on a chiral column (Chiralpak AD-H or OJ-H), and the absolute configurations were determined by comparing the optical rotation data with those reported in the literature.

To expand the synthetic scope and application of this enantioselective procedure, we also applied the optimized conditions to a variety of other α,β-unsaturated phosphonates (Fig. 2). As shown in Table 3, the β-alkyl substituted α,β-unsaturated phosphonate (*E*)-**1i** provided the hydrogenation product in good yield with 75% ee (Table 3, entry 1). In contrast, the hydrogenation of the corresponding (*Z*)-isomer ((*Z*)-**1i**), gave the opposite enantiomer with a lower ee value (Table 3, entry 2). The enantioselectivity results for substrates (*E*)-**1j** and (*E*)-**1k** were lower than that of their methyl analogue (*E*)-**1a**.

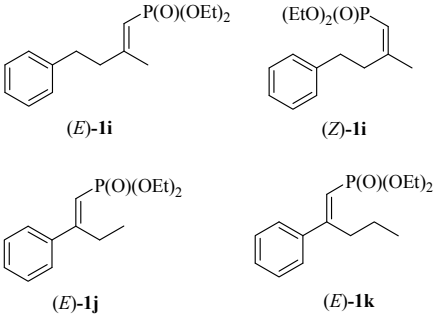
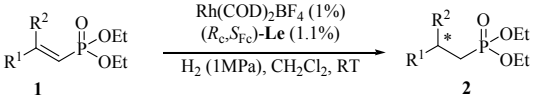


Fig. 2. Substrates for the asymmetric hydrogenation.

Table 3
Asymmetric hydrogenation of α,β-unsaturated phosphonates **1i**–**1k**.



Entry	Substrate	Yield [a] (%)	ee [b] (%)
1	(*E*)-**1i**	97	75 (–)
2	(*Z*)-**1i**	98	64 (+)
3	(*E*)-**1j**	96	69 (–)
4	(*E*)-**1k**	97	72 (–)

All reactions were carried out with 0.25 mmol of substrate at room temperature under H_2 pressure of 1 MPa in 2 ml of CH_2Cl_2 for 24 h with substrate:Rh(COD)$_2$BF$_4$:ligand = 1:0.01:0.011.

[a] Isolated yield.

[b] Determined by HPLC on a chiral column (Chiralpak AD-H or OJ-H).

Graphical Abstract

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Rh-ImiFerroPhos complexes catalyzed asymmetric hydrogenation of β-substituted α,β-unsaturated phosphonates

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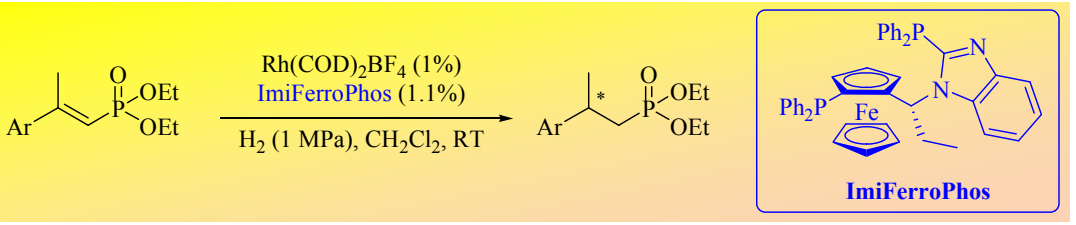

A range of optically active β-substituted alkylphosphonates have been prepared in good yields and good enantioselectivity under mild conditions via the Rh-catalyzed asymmetric hydrogenation of β-substituted α,β-unsaturated phosphonates using chiral ImiFerroPhos ligands.

4. Conclusions

We have demonstrated that (R_C,S_{Fc})-ImiFerroPhos **Le** is a suitable ligand for the Rh-catalyzed asymmetric hydrogenation of β-substituted α,β-unsaturated phosphonates, with good yield and ee value of up to 92% being obtained for a range of substrates under mild hydrogenation conditions (i.e., 1 MPa of H_2 pressure and room temperature). This catalytic system could therefore be used in a practical sense for the synthesis of optically active β-substituted alkylphosphonates. The development of new catalytic methods for the synthesis of chiral alkylphosphonates is currently underway in our laboratory.

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