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Enantioselective Synthesis of Chiral α-Aryl or α-Alkyl Substituted Ethylphosphonates via Rh-Catalyzed Asymmetric Hydrogenation with a *P*-Stereogenic BoPhoz-Type Ligand

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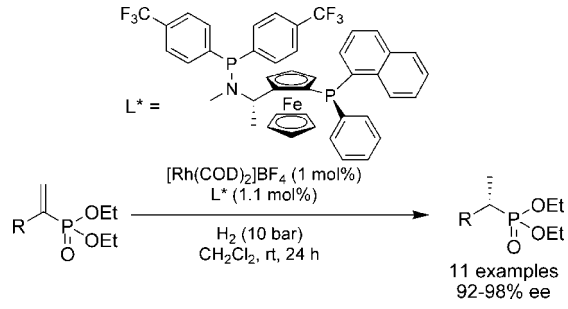

An enantioselective synthesis of optically active 1-aryl or 1-alkyl substituted ethylphosphonates, based on the first Rh-catalyzed asymmetric hydrogenation of corresponding α,β-unsaturated precursors with a *P*-stereogenic BoPhoz-type ligand under the mild condition, was developed, in which a wide range of 1-aryl or 1-alkyl substituted ethylphosphonates were achieved in up to 98% ee.

Optically active 1-arylethylphosphonates have received considerable attention in the past few years in bioorganic and medicinal chemistry[1] because of their interesting biological properties as bioisosteric derivatives of 2-arylpropionic acids such as naproxen,[2] which is a well-known nonsteroidal anti-inflammatory drug. However, achieving high enantioselectivity in the synthesis of these compounds is still a challenging task for organic chemists. The present methods for achieving the optically enriched forms of 1-arylethylphosphonates include the enantioselective methylation of benzylphosphonic acid derivatives bearing chiral auxiliaries[3] and the photo-Arbuzov rearrangement of optically active 2-(1-phenylethoxy)-1,3,2-dioxaphosphorinanes.[4] These methods, however, are not catalytic. They require stoichiometric chiral materials or special reagents that are difficult to handle. The need for the development of an efficient and catalytic method for the preparation of enantiopure 1-arylethylphosphonates is therefore apparent.[5] Recently, Genêt et al. reported that optically active 1-phenylethylphosphonic acid or its ester can be prepared by the Ru-catalyzed asymmetric hydrogenation of corresponding α,β-unsaturated precursors.[6] However, the hydrogenation required vigorous conditions (80 °C and 10 bar of H_2 for acid, 80 °C and 80 bar of H_2 for ester) and gave only moderate enantioselectivities. Using a PHOX/Ir catalyst,[7] Beletskaya, Pfaltz, and co-workers found that the hydrogenation of 1-arylethenylphosphonates could be performed under milder conditions (5 bar of H_2 and 40 °C) than the Ru-catalyzed hydrogenation and provided higher enantioselectivities. However, the substrate with a MeO group showed very low reactivity, affording only 78% conversion even after 115 h at a catalyst loading of 2 mol %. Therefore, the search for a new and versatile catalytic system for enantioselective hydrogenation of 1-arylethenylphosphonates is still a highly desirable objective.

Recently, we[8] and other groups[9] have demonstrated that the BoPhoz-type phosphine−aminophosphine ligands are highly efficient in the catalytic asymmetric hydrogenation of various

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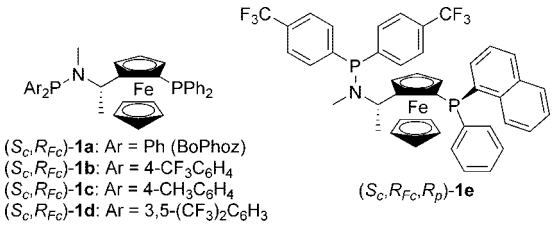


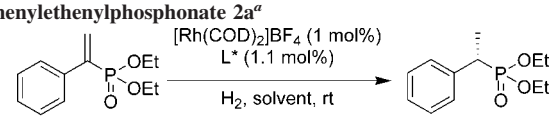
FIGURE 1. Representative structures of BoPhoz-type ligands **1a**−**e** for asymmetric hydrogenation.

prochiral C=C double bonds, especially some challenging substrates such as β^2- and γ-dehydroamino acid esters. The easily tunable property of the BoPhoz skeleton makes it an appropriate tool with which to examine the hydrogenation of these challenging substrates. For its demonstrated track record at affecting Rh-catalyzed asymmetric hydrogenations, we therefore surmise that this ligand class may be also effective for the Rh-catalyzed asymmetric hydrogenation of 1-arylethenylphosphonates. To the best of knowledge, there is still no report on the asymmetric hydrogenation of 1-arylethenylphosphonates with a chiral Rh catalyst. As a result, herein we report our results on the enantioselective synthesis of chiral 1-aryl or 1-alkyl substituted ethylphosphonates via the first Rh-catalyzed asymmetric hydrogenation with a *P*-stereogenic BoPhoz-type ligand (Figure 1), in which good enantioselectivities (up to 98% ee) were achieved for a broad range of substrates under the mild conditions.

As the substrates without or with less coordinating groups are more challenging for ruthenium- or rhodium-catalyzed asymmetric hydrogenation,[5,10,11] the difficulty in the catalytic asymmetric hydrogenation of 1-arylethenylphosphonates with a Rh catalyst can be anticipated. Our preliminary study found that most of the highly efficient and extensively used ligands in the Rh-catalyzed asymmetric hydrogenation such as DuPHOS,[12] BINAP,[13] TaniaPhos,[14] PPFAPhos,[15] and PEAPhos[16] were ineffective for this hydrogenation reaction, providing only low to moderate enantioselectivities or low catalytic activities (see Table 1, entries 1−5). In a comparison, BoPhoz proved to be a superior ligand in terms of catalytic activity and enantioselectivity.

Since the synthetic methodology of BoPhoz-type ligands is highly modular, the optimization of the BoPhoz skeleton was therefore performed, and some representative results are summarized in Table 1. Ligand screening experiment employed 1-phenylethenylphosphonate **2a** as the model substrate and was carried out in CH_2Cl_2 at room temperature under a H_2 pressure of 10 bar in the presence of 1 mol % of catalysts prepared in situ from $[Rh(COD)_2]BF_4$ and 1.1 equiv of chiral ligand. After a systematic investigation of a number of BoPhoz-type ligands, we determined that those with a trifluoromethyl group on the 4-position of the phenyl ring of aminophosphino moiety tended to give better results than that obtained with Me-BoPhoz in terms of enantioselectivity (Table 1, entries 6−10). For instance, ligand

TABLE 1. Rh-Catalyzed Asymmetric Hydrogenation of Diethyl 1-Phenylethenylphosphonate 2a[a]



2a **3a**

entry	ligand	solvent	H_2 (bar)	conversion (%)[b]	ee (%)[c]
1	Me-DuPHOS	CH_2Cl_2	10	43	17
2	BINAP	CH_2Cl_2	10	33	32
3	TaniaPhos	CH_2Cl_2	10	>95	17
4	PPFAPhos	CH_2Cl_2	10	>95	12
5	PEAPhos	CH_2Cl_2	10	>95	77
6	(S_c,R_{Fc})-**1a**	CH_2Cl_2	10	>95	86
7	(S_c,R_{Fc})-**1b**	CH_2Cl_2	10	>95	89
8	(S_c,R_{Fc})-**1c**	CH_2Cl_2	10	81	87
9	(S_c,R_{Fc})-**1d**	CH_2Cl_2	10	>95	70
10	(S_c,R_{Fc},R_p)-**1e**	CH_2Cl_2	10	>95	95
11	(S_c,R_{Fc},R_p)-**1e**	MeOH	10	20	*d*
12	(S_c,R_{Fc},R_p)-**1e**	*i*-PrOH	10	>95	18
13	(S_c,R_{Fc},R_p)-**1e**	THF	10	50	*d*
14	(S_c,R_{Fc},R_p)-**1e**	PhMe	10	<5	*d*
15	(S_c,R_{Fc},R_p)-**1e**	CH_2Cl_2	5	>95	92
16	(S_c,R_{Fc},R_p)-**1e**	CH_2Cl_2	20	>95	95
17	(S_c,R_{Fc},R_p)-**1e**	CH_2Cl_2	50	>95	92[e]
18	(S_c,R_{Fc},R_p)-**1e**	CH_2Cl_2	10	<5	*f*

[a] All reactions were performed with 0.25 mmol of substrate **2a** at room temperature under an indicated H_2 pressure in 2 mL of solvent for 24 h unless otherwise specified. Substrate/$[Rh(COD)_2]BF_4$/ligand = 1/0.01/0.011. [b] Conversions were determined by ^1H NMR. [c] The ee values were determined by HPLC on a chiral column (chiralpak AD-H, 40 °C, 215 nm, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min). [d] Not determined because of low conversions. [e] Reaction was performed at a catalyst loading of 0.2 mol %. [f] $[Rh(COD)Cl]_2$ was used as catalyst precursor.

1b with a CF_3 group on the 4-position of the phenyl ring gave 89% ee and full conversions in the hydrogenation of **2a**, while the presence of a 4-Me substituent in the phenyl ring of ligand resulted in a reduced enantioselectivity and reactivity (Table 1, entries 7 and 8). However, the introduction of two CF_3 groups onto the 3,5-positions of the phenyl ring resulted in a decreased enantioselectivity (Table 1, entry 9). In particular, ligand (S_c,R_{Fc},R_P)-**1e**, bearing a stereogenic *P* center in the phosphino moiety and a 4-CF_3 group on the phenyl ring of aminophosphino moiety, provided the best enantioselectivity of up to 95% ee (Table 1, entry 10). Subsequent experiments in an effort to attain higher enantioselectivities by optimizing the reaction conditions proved unfruitful. As shown in Table 1, strong solvent dependency was observed in the reaction. However, no results surpassed that obtained in CH_2Cl_2 (Table 1, entries 10−14). Lowering or elevating H_2 pressure could not improve enantioselectivity (Table 1, entries 15 and 16). Reducing the catalyst loading to 0.2 mol % also provided good enantioselectivity (92% ee); however, an elevated H_2 pressure (50 bar) was required to complete the hydrogenation (Table 1, entry 17). Using $[Rh(COD)Cl]_2$ as the catalyst precursor resulted in extremely low catalytic activity (Table 1, entry 18).

To demonstrate the flexibility of the present catalytic system, we subsequently examined the hydrogenation of a series of 1-arylethenylphosphonates **2a**−**l** under the optimized conditions (1 mol % of catalyst loading prepared in situ from $[Rh(COD)_2]BF_4$ and 1.1 equiv of ligand **1e**, performed under 10 bar of H_2 pressure in CH_2Cl_2 at room temperature for 24 h), and the results are summarized in Table 2. Initially, the effect of the ester function in α,β-unsaturated phosphonates was evaluated, and a series of 1-phenylethenylphosphonates **2a**−**c**

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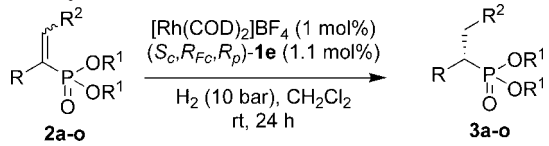
TABLE 2. Asymmetric Hydrogenation of Substrates 2a−o Using Rh/(S_c,R_{Fc},R_p)-1e Catalyst[a]



entry	substrate (R, R^1, R^2)	yield (%)	ee (%)[b]
1	**2a** (Ph, Et, H)	95	95 (*S*)
2	**2b** (Ph, Me, H)	91	93 (−)
3	**2c** (Ph, *i*-Pr, H)	96	95 (−)
4	**2d** (*o*-$MeOC_6H_4$, Et, H)	98	94 (+)
5	**2e** (*m*-$MeOC_6H_4$, Et, H)	96	96 (−)
6	**2f** (*p*-$MeOC_6H_4$, Et, H)	92	96 (−)
7	**2g** (*p*-FC_6H_4, Et, H)	96	95 (−)
8	**2h** (*p*-ClC_6H_4, Et, H)	99	94 (−)
9	**2i** (*p*-BrC_6H_4, Et, H)	99	95 (−)
10	**2j** (*p*-MeC_6H_4, Et, H)	96	95 (*S*)
11	**2k** (1-naphthyl, Et, H)	97	92 (+)
12	**2l** (6-methoxy-2-naphthyl, Et, H)	99	97 (−)
13	**2m** (*i*-Pr, Et, H)	95	98 (+)
14	(*E*)-**2n** (Ph, Et, Et)	95	29 (−)[c]
15	**2o** (*p*-FC_6H_4, H, H)	−	*d*

[a] All reactions were performed with 0.25 mmol of substrates **2a−o** at room temperature under a H_2 pressure of 10 bar in 2 mL of CH_2Cl_2 for 24 h. Substrate/$[Rh(COD)_2]BF_4$/ligand = 1/0.01/0.011. Full conversions were obtained in all cases except **2o**. [b] The ee values were determined by HPLC or GC on a chiral column. The absolute configuration was determined by comparing the sign of optical rotation with reported data or by comparison of chiral HPLC elution order with configurationally defined examples. [c] Reaction was performed under a H_2 pressure of 60 bar. [d] Not determined because of low conversions.

with the different ester group were submitted to this hydrogenation. The results indicated that the ester function has little influence on the enantioselectivity, and all of 1-phenylethenylphosphonates **2a−c** were hydrogenated in high enantioselectivities (Table 2, entries 1−3). A range of diethyl 1-arylethenylphosphonates **2d−l** were then prepared and employed in this hydrogenation. In all cases, the hydrogenation proceeded to completion and provided the corresponding hydrogenation product with high enantioselectivities (92−97% ee) as well as good to excellent yields (Table 2, entries 4−12). The results revealed that there is no major effect on the substitution pattern of the substituent on the phenyl ring of substrates. For examples, all of three substrates with a methoxy group on the phenyl ring were hydrogenated in 94−96% ee (Table 2, entries 4−6). Among all of the substrates with a *para*-substituent tested, diethyl 1-(4-methoxyphenyl)ethenylphosphonate **2f** was hydrogenated with the best enantioselectivity of 96% ee (Table 2, entry 6). Good enantioselectivity (92% ee) was also observed in the hydrogenation of 1-naphthyl substituted substrate **2k** (Table 2, entry 11). In particular, diethyl 1-(6-methoxy-1-naphthyl)ethenylphosphonate **2l**, which showed low reactivity in the Ir-catalyzed asymmetric hydrogenation, was completely hydrogenated in excellent enantioselectivity (97% ee) (Table 2, entry 12). 1-Alkyl substituted substrate **2m** was also hydrogenated in 98% ee and 95% yield (Table 1, entry 13). These results demonstrated the high efficiency of the present catalytic system, representing the best results reported so far. However, the present catalytic system is not efficient for the hydrogenation of trisubstituted substrates (e.g., (*E*)-**2n**) (Table 1, entry 14). For the hydrogenation of phosphonic acid substrate **2o**, low reactivity was observed (Table 1, entry 15).

In conclusion, we have disclosed that a series of chiral 1-aryl or 1-alkyl substituted ethylphosphonates could be synthesized in high enantioselectivities (92−98% ee) and excellent yields in the first Rh-catalyzed asymmetric hydrogenation of corresponding 1-aryl or 1-alkylethenylphosphonates using a *P*-stereogenic chiral BoPhoz-type phosphine−aminophosphine ligand. Hydrogenation can be performed under the mild conditions (10 bar of H_2 pressure and room temperature) and relatively low catalyst loading (up to 0.2 mol %), which represented the best result in the catalytic asymmetric synthesis of chiral 1-aryl or 1-alkyl substituted ethylphosphonates reported so far. It is our hope that this work will provide a new and practical method to prepare chiral 1-substituted ethylphosphonates and their derivatives.

Experimental Section

1-Substituted ethenylphosphonates **2a−m** and (*E*)-1-phenylbutenylphosphonate **2n** were prepared according to the known methods.[6,7,17]

General Hydrogenation Procedure. To a solution of $[Rh(COD)_2]BF_4$ (1.0 mg, 0.0025 mmol) in 1 mL of CH_2Cl_2, which was placed in a nitrogen-filled glovebox, was added 1.1 equiv of ligand (S_c,R_{Fc},R_P)-**1e**. The mixture was stirred at room temperature for 30 min, and then a solution of a substrate (0.25 mmol) in 1 mL of CH_2Cl_2 was added. The reaction mixture was transferred to a Parr stainless autoclave. The autoclave was purged three times with hydrogen and maintained a hydrogen pressure of 10 bar. The hydrogenation was performed at room temperature for 24 h. After carefully releasing the hydrogen, the solvent was removed. The residue was filtered through a short SiO_2 column to remove the catalyst. The filtrate was concentrated under reduced pressure, and the enantiomeric excess was determined by HPLC on a chiral column.

Diethyl 1-Phenylethylphosphonate (3a):[6] colorless oil; 95% ee; $[\alpha]^{25}_D = -7.6$ (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, J = 6.9 Hz, 3H), 1.27 (t, J = 6.9 Hz, 3H), 1.58 (dd, J = 17.9, 7.0 Hz, 3H), 3.19 (dq, J = 22.0, 7.0 Hz, 1H), 3.79 (m, 1H), 3.92 (m, 1H), 4.03 (m, 2H), 7.24 (t, J = 6.9 Hz, 1H), 7.29−7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 16.3, 16.4, 38.6 (d, J = 136 Hz), 61.9, 62.4, 127.0, 128.4, 128.7, 138.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.2; HPLC (Chiralpak AD-H, elute = 5% *i*-propanol/95% *n*-hexane, flow rate = 1.0 mL/min, detector = 215 nm), (*S*) t_1 = 7.56 min; (*R*) t_2 = 8.98 min.

Diethyl 1-(6-methoxy-2-naphthyl)ethylphosphonate (3l):[7] white solid, mp 58−59 °C; 97% ee; $[\alpha]^{25}_D = -16.0$ (1.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (t, J = 6.9 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.65 (dd, J = 18.2, 7.2 Hz, 3H), 3.31 (dq, J = 22.4, 7.2 Hz, 1H), 3.77 (m, 1H), 3.89−3.94 (m, 4H), 4.03 (m, 2H), 7.10−7.14 (m, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.69−7.771 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 16.3 (d, J = 5 Hz), 16.5 (d, J = 5 Hz), 38.4, 55.3, 61.9 (d, J = 6 Hz), 62.4 (d, J = 6 Hz), 105.6, 118.9, 126.8, 127.1 (d, J = 8 Hz), 127.5 (d, J = 4 Hz), 128.9, 129.3, 133.2 (d, J = 6 Hz), 133.7, 157.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.2; HPLC (Chiralpak AD-H, elute = 5% *i*-propanol/95% *n*-hexane, flow rate = 1.0 mL/min, detector = 215 nm), (*S*) t_1 = 20.88 min; (*R*) t_2 = 33.03 min.

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Supporting Information Available: ^{1}H, ^{31}P, and ^{13}C NMR spectra, and analysis of ee values of the hydrogenation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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