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# Highly Enantioselective Rh-Catalyzed Hydrogenation of $\beta,\gamma$-Unsaturated Phosphonates with Chiral Ferrocene-Based Monophosphoramidite Ligands

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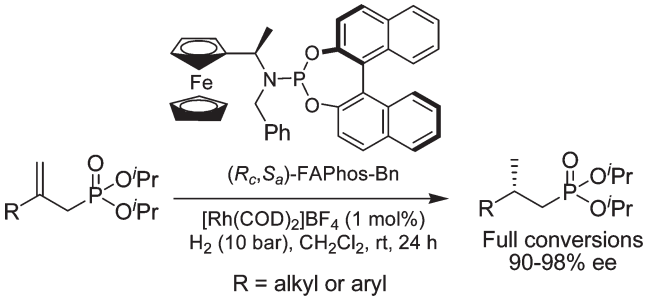


An enantioselective synthesis of chiral alkylphosphonates bearing a $\beta$-stereogenic center, based on the Rh-catalyzed asymmetric hydrogenation of corresponding $\beta$-substituted $\beta,\gamma$-unsaturated phosphonates with a ferrocene-based monophosphoramidite ligand under the mild hydrogenation conditions, was developed, in which an ee value of up to 98% was obtained.

Optically active alkylphosphonic acid derivatives are biologically active compounds and useful building blocks in organic synthesis.[1] However, methods for the catalytic enantioselective synthesis of chiral alkylphosphonates, in particular those bearing a $\beta$-stereogenic center, is still rare, although such a process holds the potential of providing chiral alkylphosphonic acid derivatives with high efficiency. Therefore, the development of new catalytic methods for the enantioselective synthesis of these compounds is highly desirable. We envision that the catalytic asymmetric hydrogenation of the corresponding prostereogenic 2-arylallylphosphonates should be one of the most effective methods for the construction of these moieties because of its inherent efficiency and atom economy. Although significant progress has been made in the catalytic asymmetric hydrogenation of α-arylethenylphosphonates[3] and other α,$\beta$-unsaturated phosphonates[4] with various Rh, Ru, or Ir complexes, the asymmetric hydrogenation of $\beta,\gamma$-unsaturated phosphonates remains unexplored. Herein we report for the first time a highly enantioselective rhodium-catalyzed hydrogenation of $\beta$-substituted $\beta,\gamma$-unsaturated phosphonates with a 1-ferrocenylethylamine-derived monodentate phosphoramidite ligand, with which a variety of chiral $\beta$-aryl-substituted propylphosphonates were prepared in 90−98% ee.

A family of prostereogenic $\beta$-substituted $\beta,\gamma$-unsaturated phosphonates **4** was prepared from propargyl alcohol **1** through a simple and versatile synthetic method as shown in Scheme 1. Initially, propargyl alcohol **1** underwent

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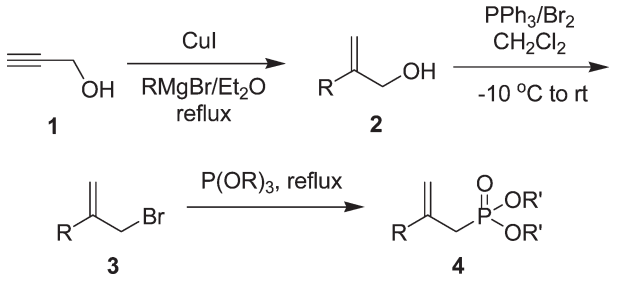
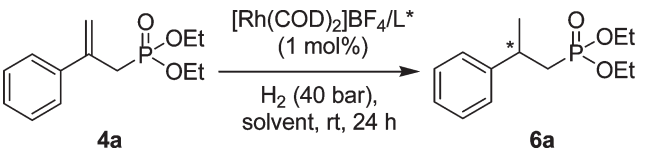
**SCHEME 1. Synthesis of $\beta$-Substituted $\beta,\gamma$-Unsaturated Phosphonates 4**




region-specific additions of Grignard reagents in the presence of CuI to yield allylic alcohols **2**.[5] By treatment with $PPh_3/Br_2$ in $CH_2Cl_2$, alcohols **2** were transformed into allylic bromides **3** in high yields. The reaction of allylic bromides **3** with various trialkyl phosphites at refluxing temperature gave the target 2-substituted allylphosphonates **4** in good yields.

With easy access to the substrates **4**, the key to achieving high enantioselectivities for this asymmetric hydrogenation therefore is to find an efficient catalyst. We initiated our studies on the Rh-catalyzed asymmetric hydrogenation of diethyl 2-phenylallylphosphonate **4a** by briefly screening several chiral phosphorus ligands. Hydrogenations were performed in $CH_2Cl_2$ at room temperature under a $H_2$ pressure of 40 bar in the presence of 1 mol % of catalysts prepared in situ from $[Rh(COD)_2]BF_4$ and chiral ligand. The preliminary results in Table 1 revealed that most of the highly efficient and extensively used ligands in the Rh-catalyzed asymmetric hydrogenation such as BoPhoz,[8] BINAP,[9] TaniaPhos,[10] WalPhos,[11] DuPHOS,[12] and PPFAPhos[13] are not effective for this hydrogenation in term of enantioselectivity or reactivity (Table 1, entries 1−6). Interestingly, ($R_c$,$S_a$)-FAPhos **5** (Figure 1), a new class of monophosphoramidite ligands recently developed by us for the Rh-catalyzed asymmetric hydrogenation of a variety of prochiral C=C bonds, displayed promising results. The results disclosed that the substituent in the amino moiety of FAPhos had a dramatic effect on the enantioselectivity, and a ligand containing a bulkier substituent in the amino moiety tended to provide higher levels of enantioselectivity. Thus, replacing the methyl group of ($R_c$,$S_a$)-FAPhos **5a** with an ethyl group led to the enantioselectivity dramatically rising from 52% ee to 90% ee (Table 1, entries 7 and 8). Using ($R_c$,$S_a$)-FAPhos **5c** containing a benzyl group further increased the enantioselectivity to 94% ee (Table 1, entry 9). A comparison of the results

**TABLE 1. Rh-Catalyzed Asymmetric Hydrogenation of Diethyl 2-Phenylallylphosphonate 4a[a]**




| entry | ligand | solvent | $H_2$ (bar) | conversion (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | BoPhoz | $CH_2Cl_2$ | 40 | 100 | 69 |
| 2 | BINAP | $CH_2Cl_2$ | 40 | 63 | 23 |
| 3 | TaniaPhos | $CH_2Cl_2$ | 40 | 100 | 26 |
| 4 | WalPhos | $CH_2Cl_2$ | 40 | 100 | 78 |
| 5 | Me-DuPHOS | $CH_2Cl_2$ | 40 | 92 | 41 |
| 6 | PPFAPhos | $CH_2Cl_2$ | 40 | 100 | 42 |
| 7 | ($R_c$,$S_a$)-**5a** | $CH_2Cl_2$ | 40 | 100 | 52 |
| 8 | ($R_c$,$S_a$)-**5b** | $CH_2Cl_2$ | 40 | 100 | 90 |
| 9 | ($R_c$,$S_a$)-**5c** | $CH_2Cl_2$ | 40 | 100 | 94 |
| 10 | ($R_c$,$R_a$)-**5d** | $CH_2Cl_2$ | 40 | 100 | 78 |
| 11 | ($R_c$,$S_a$)-**5c** | MeOH | 40 | 82 | 81 |
| 12 | ($R_c$,$S_a$)-**5c** | *i*-PrOH | 40 | 95 | 85 |
| 13 | ($R_c$,$S_a$)-**5c** | THF | 40 | 52 | [d] |
| 14 | ($R_c$,$S_a$)-**5c** | PhMe | 40 | 29 | [d] |
| 15 | ($R_c$,$S_a$)-**5c** | $CH_2Cl_2$ | 10 | 100 | 93 |

[a]Hydrogenations were performed with 0.25 mmol of substrate **4a** at room temperature under a $H_2$ pressure of 40 bar in 2 mL of solvent for 24 h unless otherwise specified. Substrate/$[Rh(COD)_2]BF_4$/ligand = 1/0.01/0.011−0.022. [b]Conversions were determined by GC. [c]The ee values were determined by HPLC on a chiral column. [d]Not determined.

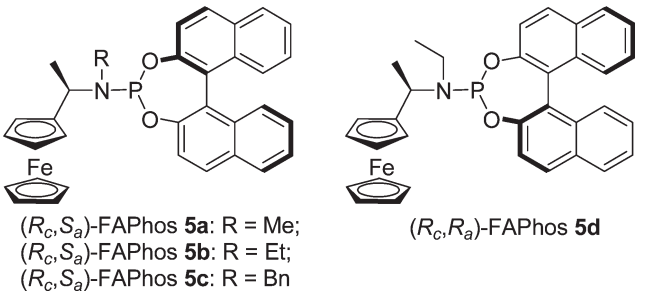



**FIGURE 1.** Ferrocene-based monophosphoramidite ligands, FAPhos **5**, for asymmetric hydrogenation.

obtained with ($R_c$,$S_a$)-FAPhos **5b** and ($R_c$,$R_a$)-FAPhos **5d** revealed that the binaphthyl moiety in these ligands controls the chirality of the hydrogenation product and the matched stereogenic elements are ($R_c$)-central and ($S_a$)-axial absolute configurations (Table 1, entries 8 and 10). Subsequent investigation on the optimization of the hydrogenation condition disclosed that the nature of the solvent had a significant effect in this hydrogenation. However, no result surpassed that obtained in $CH_2Cl_2$ (Table 1, entries 11−14). Lowering $H_2$ pressure to 10 bar also provided good enantioselectivity (Table 1, entry 15).

Having established ($R_c$,$S_a$)-FAPhos **5c** as the optimal ligand, we next investigated the effect of the ester functional group of $\beta,\gamma$-unsaturated phosphonates on enantioselectivity. The results are summarized in Table 2. It is very interesting that a modest change from a methyl ester (**4b**) to an ethyl ester (**4a**) led to the dramatically increased enantioselectivity (Table 2, entries 1 and 2). The introduction of a bulkier *i*-Pr ester functional group further increased the enantioselectivity to 97% ee (Table 2, entry 3). These results

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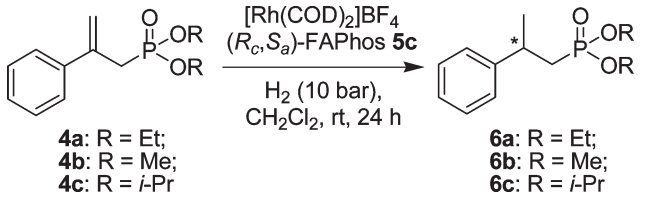
**TABLE 2. Effect of Ester Functional Group of 2-Phenylallylphosphonates on Enantioselectivity[a]**



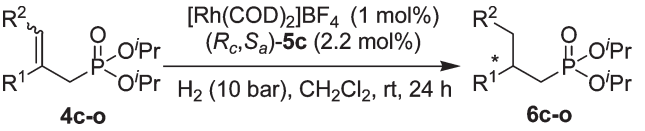

| entry | substrate (R) | conversion (%)[b] | ee (%)[c] |
|---|---|---|---|
| 1 | **4b** (R = Me) | 100 | 54 |
| 2 | **4a** (R = Et) | 100 | 92 |
| 3 | **4c** (R = *i*-Pr) | 100 | 97 |
| 4 | **4c** (R = *i*-Pr) | 100 | 96[d] |

[a]Hydrogenations were performed with 0.25 mmol of substrate at room temperature under a $H_2$ pressure of 10 bar in 2 mL of $CH_2Cl_2$ for 24 h unless otherwise specified. Substrate/$[Rh(COD)_2]BF_4$/($R_c$,$S_a$)-**5c** = 1/0.01/0.011. [b]Conversions were determined by GC. [c]The ee values were determined by HPLC on a chiral column. [d]Reaction was performed at a catalyst loading of 0.2 mol % under a $H_2$ pressure of 20 bar.

suggested that the ester functional group of $\beta,\gamma$-unsaturated phosphonates has a significant influence on the enantioselectivity, and the substrate with a bulkier ester group tended to give higher enantioselectivity. Reducing the catalyst loading to 0.2 mol % did not impact enantioselectivity but required an elevated $H_2$ pressure of 20 bar to complete the hydrogenation (Table 2, entry 4). Further decrease of the catalyst loading under the same hydrogenation condition resulted in incomplete conversion.

Catalytic asymmetric synthesis of chiral $\beta$-substituted propylphosphonates is still rarely explored. The first example, based on the Rh-catalyzed asymmetric 1,4-addition to 1-alkenylphosphonates using arylboroxines as arylating reagents, was reported by Hayashi et al. in 1999, in which a variety of chiral $\beta$-arylalkylphosphonates were achieved in good enantioselectivities.[2a] However, this method has the disadvantages of the use of the expensive reagent and high catalyst loadings. To demonstrate the potential of the present catalytic system, a series of $\beta,\gamma$-unsaturated phosphonates with a *i*-Pr ester functional group were then prepared and subjected to this hydrogenation under the optimized conditions (1 mol % of catalyst loading prepared in situ from $[Rh(COD)_2]BF_4$ and 2.2 equiv of ($R_c$,$S_a$)-FAPhos **5c**, performed under 10 bar of $H_2$ pressure in $CH_2Cl_2$ at room temperature for 24 h). As shown in Table 3, full conversions and high yields were achieved in all cases. The results indicated that the electronic nature and the substitution pattern of the substituent on the phenyl ring of substrates had no major effect on the enantioselectivities. All of the substrates with the different substituent in the phenyl ring were hydrogenated with high enantioselectivities (Table 3, entries 2−8). In the hydrogenation of the substrate **4k** with a $\beta$-1-naphthyl substituent, an ee value of 97% was obtained (entry 9). The hydrogenation of $\beta$-heteroaromatic thienyl and $\beta$-alkyl substituted substrates **4l**−**n** also led to good enantioselectivities (Table 3, entries 10−12). These results demonstrate the high efficiency of the present catalytic system in the catalytic hydrogenation of this new substrate class. However, for the hydrogenation of trisubstituted olefin (*Z*)-**4o** under the optimized conditions, the present

**TABLE 3. Rh-Catalyzed Asymmetric Hydrogenation of Di-isopropyl 2-Substituted Allylphosphonates 4c−o with ($R_c$,$S_a$)-FAPhos 5c [a]**




| entry | substrate (R) | yield (%) | ee (%)[b] |
|---|---|---|---|
| 1 | **4c** ($R^1$ = Ph, $R^2$ = H) | 98 | 97 (*S*); |
| 2 | **4d** ($R^1$ = 2-MeO$C_6H_4$, $R^2$ = H) | 98 | 95 (−); |
| 3 | **4e** ($R^1$ = 3-MeO$C_6H_4$, $R^2$ = H) | 98 | 97 (−); |
| 4 | **4f** ($R^1$ = 4-MeO$C_6H_4$, $R^2$ = H) | 99 | 98 (−); |
| 5 | **4g** ($R^1$ = 4-Me$C_6H_4$, $R^2$ = H) | 96 | 97 (−); |
| 6 | **4h** ($R^1$ = 3-$CF_3C_6H_4$, $R^2$ = H) | 97 | 97 (−); |
| 7 | **4i** ($R^1$ = 4-$CF_3C_6H_4$, $R^2$ = H) | 93 | 95 (−); |
| 8 | **4j** ($R^1$ = 4-F$C_6H_4$, $R^2$ = H) | 95 | 96 (−); |
| 9 | **4k** ($R^1$ = 1-naphthyl, $R^2$ = H) | 91 | 97 (+); |
| 10 | **4l** ($R^1$ = 2-thienyl, $R^2$ = H) | 96 | 90 (−); |
| 11 | **4m** ($R^1$ = $PhCH_2$, $R^2$ = H) | 99 | 96 (−); |
| 12 | **4n** ($R^1$ = *n*-$C_4H_9$, $R^2$ = H) | 98 | 96 (*S*); |
| 13 | (*Z*)-**4o** ($R^1$ = Ph, $R^2$ = Me) | 97 | 61 (−)[c] |

[a]Hydrogenations were carried out with 0.25 mmol of substrate at room temperature under a $H_2$ pressure of 10 bar in 2 mL of $CH_2Cl_2$ for 24 h unless otherwise specified. Substrate/$[Rh(COD)_2]BF_4$/($R_c$,$S_a$)-**5c** = 1/0.01/0.022. Full conversions were achieved in all cases. [b]The ee values were determined by HPLC on a chiral column. [c]Hydrogenation was performed at a catalyst loading of 5 mol % under a $H_2$ pressure of 60 bar.

catalytic system gave only low conversion. Full conversion and moderate enantioselectivity were achieved under a $H_2$ pressure of 60 bar in the presence of 5 mol % of catalyst (entry 13).

In conclusion, we have found that a series of chiral $\beta$-substituted 1-propylphosphonates could be synthesized in high enantioselectivities (90−98% ee) by a Rh-catalyzed asymmetric hydrogenation of $\beta$-substituted $\beta,\gamma$-unsaturated phosphonates using a ferrocene-based monophosphoramidite ligand, ($R_c$,$S_a$)-FAPhos **5c** under the mild conditions (10 bar of $H_2$ pressure and room temperature). The research suggested that the ester functional group of $\beta,\gamma$-unsaturated phosphonates has a significant influence on the enantioselectivity, and the substrate with a bulkier ester group tended to give higher enantioselectivity. It is our hope that the present work will provide a new and practical method to prepare chiral 2-substituted alkylphosphonate derivatives.

## Experimental Section

**General Procedure for the Preparation of 2-Substituted Allylphosphonates.** To a solution of RMgBr (50 mmol) in 120 mL of $Et_2O$ was added CuI (0.57 g, 3.0 mmol). The mixture was stirred at room temperature for 0.5 h, and then a solution of propargyl alcohol (1.12 g, 20 mmol) in 20 mL of $Et_2O$ was added slowly. After the addition was complete, the reaction mixture was refluxed for 24 h. After cooling to room temperature, an aqueous solution of saturated $NH_4Cl$ was added slowly. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$. The organic layer was combined and dried over anhydrous $Na_2SO_4$. After removal of the volatiles, the residue was purified by column chromatography (silica gel, AcOEt/*n*-hexane, 10/1) to give allylic alcohols **2**.

Bromine (1.76 g, 11 mmol) was added to a solution of $PPh_3$ (3.14 g, 12 mmol) in 15 mL of $CH_2Cl_2$ over 10 min, maintaining the temperature below −10 °C. A solution of allylic alcohols **2** (10 mmol) in 5 mL of $CH_2Cl_2$ was added, and the mixture was

allowed to warm to 10 °C over 20 min. The mixture was diluted with pentane (50 mL) and filtered through a plug composed of silica (25 g) layered over neutral alumina (25 g). The plug was washed with pentane/ether (30:1), and the combined filtrates were evaporated to provide the crude allylic bromides **3**, which can be used directly for the next step without further purification.

A solution of allylic bromides **3** (5 mol) in trialkyl phosphites (15 mol) was heated to reflux and stirred at the same temperature for 3 h. Excess trialkyl phosphite and the side product were removed in vacuo. Flash chromatography of the residue on silica gel (AcOEt/hexane, 1:1) gave the target allylphosphonates **4**.

**Di-isopropyl 2-Phenylallylphosphonate (4c).** Yield: 50%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.17 (d, $J$ = 5.7 Hz, 6H), 1.25 (d, $J$ = 5.7 Hz, 6H), 3.01 (d, $J$ = 22.2 Hz, 2H), 4.60−4.67 (m, 2H), 5.35 (d, $J$ = 5.2 Hz, 1H), 5.50 (d, $J$ = 5.2 Hz, 1H), 7.24−7.33 (m, 3H), 7.45−7.47 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 23.7 (d, $J$ = 5.0 Hz), 24.0 (d, $J$ = 3.0 Hz), 34.0 (d, $J$ = 140.0 Hz), 70.5 (d, $J$ = 6.0 Hz), 117.0 (d, $J$ = 11.0 Hz), 126.4, 127.6, 128.2, 139.0 (d, $J$ = 10.0 Hz), 140.9 (d, $J$ = 4.0 Hz). $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 24.9. HRMS calcd for $C_{15}H_{23}O_3NaP$ [M + Na]: 305.1283, found 305.1290.

**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 2.2 equiv of ligand ($R_c$,$S_a$)-FAPhos **5c**. The mixture was stirred at room temperature for 30 min, and then was added a solution of a substrate (0.25 mmol) in 1 mL of $CH_2Cl_2$. The reaction mixture was transferred to a Parr stainless autoclave. The autoclave was purged three times with hydrogen, and a hydrogen pressure of 10 bar was maintained. 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.

**Di-isopropyl 2-Phenyl-1-propylphosphonate (6c).** 97% ee. $[\alpha]^{25}_D$ = −14.4 ($c$ 1.2, $CHCl_3$). HPLC conditions: chiralcel AD-H, 40 °C, $n$-hexane/isopropyl alcohol = 98/2, flow rate = 1.0 mL/min, $t_1$ = 13.8 min; $t_2$ = 12.7 min. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.19 (d, $J$ = 6.2 Hz, 3H), 1.24 (d, $J$ = 6.2 Hz, 3H), 1.27 (d, $J$ = 6.2 Hz, 3H), 1.28 (d, $J$ = 6.2 Hz, 3H), 1.39 (d, $J$ = 7.2 Hz, 3H), 1.97−2.07 (m, 2H), 3.17−3.21 (m, 1H), 4.59−4.67 (m, 2H), 7.17−7.23 (m, 3H), 7.27−7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 23.4 (d, $J$ = 8.0 Hz), 23.9 (d, $J$ = 5.0 Hz), 24.0 (d, $J$ = 5.0 Hz), 34.8, 35.7 (d, $J$ = 139.0 Hz), 69.9 (d, $J$ = 7.0 Hz), 70.0 (d, $J$ = 7.0 Hz), 126.3, 126.7, 128.5, 147.1 (d, $J$ = 13.0 Hz). $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 28.6. HRMS calcd for $C_{15}H_{25}O_3P$: 284.1541, found 284.1548.

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**Supporting Information Available:** $^1$H, $^{31}$P and $^{13}$C NMR spectra of **4c**−**o** and **6c**−**o**, and analysis of ee values of the hydrogenation products **6a**−**o**. This material is available free of charge via the Internet at http://pubs.acs.org.