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Enantioselective Rh-Catalyzed Hydrogenation of 3-Aryl-4-phosphonobutenoates with a *P*-Stereogenic BoPhoz-Type Ligand

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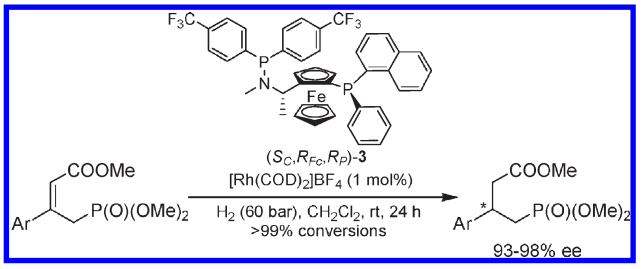
Received September 18, 2010



A series of chiral 3-aryl-4-phosphonobutyric acid esters were synthesized in high enantioselectivities (93−98% ee) via the Rh-catalyzed asymmetric hydrogenation of the corresponding 3-aryl-4-phosphonobutenoates using a *P*-stereogenic BoPhoz-type phosphine−aminophosphine ligand. The methodology has been successfully applied to the asymmetric synthesis of a potential $GABA_B$ antagonist, (*R*)-phaclofen, in high enantioselectivity.

Optically active phosphonates, as isosteres of carboxylates, are important substrates in the study of biochemical processes and reveal diverse and interesting biological and biochemical properties in their role as enzyme inhibitors, agrochemicals, or pharmaceuticals.[1] The enantioselective access to these compounds, in particular by a catalytic method, has therefore drawn a great deal of attention in the past few decades.[2] Given its inherent efficiency and atom economy, the catalytic asymmetric hydrogenation of prochiral phosphonate derivatives is certainly one of the simplest and the most efficient approaches to prepare chiral phosphonates. Indeed, such methods are among the most studied and widely applied for the enantioselective preparation of a variety of α- or *β*-substituted phosphonic acid derivatives (i.e., α-hydroxyphosphonates,[3] α-aminophosphonates,[4] α-alkylphosphonates,[5] and 3-phosphonopropanoic acid derivatives[6]). To the best of our knowledge, however, enantioselective synthesis of 4-phosphonobutyric acid derivatives via the catalytic enantioselective hydrogenation with chiral metal complexes remains an unexplored area. These kinds of chiral compounds are very useful precursors to other optically active phosphonic acid derivatives such as 3-aminopropane-1-phosphonic acids, which are potential $GABA_B$ antagonists. Herein, we describe the first highly enantioselective synthesis of a series of chiral 3-aryl-4-phosphonobutyric acid esters via a rhodium-catalyzed asymmetric hydrogenation with a *P*-stereogenic Bophoz-type phosphine−aminophosphine ligand.

The basic strategy for the synthesis of chiral 3-substituted 4-phosphonobutyric acid esters involved asymmetric hydrogenation of the corresponding 4-phosphonobutenoates. The latter can be easily prepared from ketones through a three-step transformation as outlined in Scheme 1. Initially, the unsaturated esters were obtained by the Horner−Wittig reaction, in which (*E*)-isomers were formed predominantly.[7] Bromination

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DOI: 10.1021/jo101849b Published on Web 11/09/2010

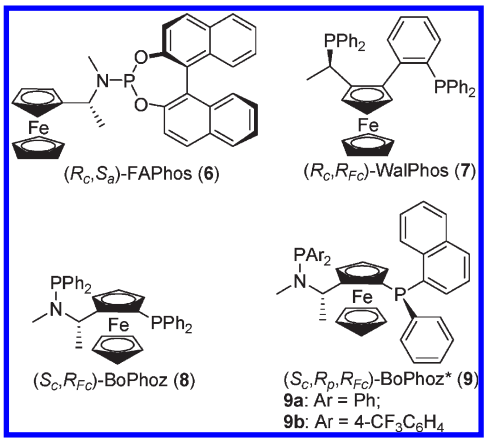
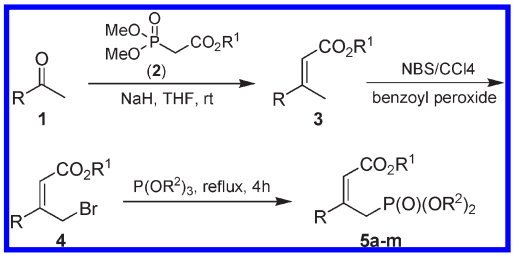


FIGURE 1. Structure of ligands for asymmetric hydrogenation.

SCHEME 1. Synthesis of 4-Phosphonobutenoates 5a−m

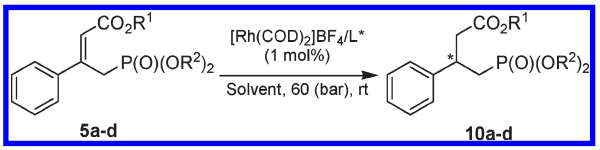


of (*E*)-**3** with *N*-bromosuccinimide in the presence of benzoyl peroxide gave the allylic bromides (**4**) in high yields. The Arbusov reaction with phosphites gave the target phosphonates **5**.

With these substrates in hand, we attempted to find an efficient catalyst for the highly enantioselective hydrogenation of these 4-phosphonobutenoic acid esters. We focused our efforts on searching for an appropriate chiral phosphorus ligand for their demonstrated track record at affecting Rh-catalyzed asymmetric hydrogenations of phosphonates. Initially, 4-(diisopropoxyphosphoryl)-3-phenylbut-2-enoic acid isopropyl ester **5a** was employed as the standard substrate in the ligand screening with a diverse array of chiral phosphorus-containing ligands, which are commercially available or developed within our research group. A few representative ligands screened are shown in Figure 1. Surprisingly, poor enantioselectivity (25% ee) was obtained for a (R_c,S_a)-FAPhos **6**, which was effective for the hydrogenation of unfunctionalized β,γ-unsaturated phosphonates (Table 1, entry 1).[8] (R_c,R_{Fc})-WalPhos **7** offered full conversion but low enantioselectivity (< 10% ee) (entry 2).[9] While (S_c,R_{Fc})-BoPhoz **8** displayed poor performance (entry 3),[10] higher conversion and better enantioselectivity were achieved with a modified BoPhoz-type ligand **9a** bearing a *P*-stereogenic center (entry 4).[11] Subsequent optimization of the BoPhoz* skeleton disclosed that ligand **9b** with a CF_3 group on the 4-position of the phenyl ring gave the best result (entry 5). Having established the optimal ligand, we next investigated the effect of the ester group of phosphonates on this hydrogenation. The results indicated that the ester group had a significant effect in enantioselectivities, and the substrate with the less sterically demanding ester group tended to give better result (entries 5−8). When 4-(dimethoxyphosphoryl)-3-phenylbut-2-enoic acid methyl ester **5d** was used as the hydrogenation substrate, excellent enantioselectivity (98%) was achieved (entry 8). We also screened several solvents for the reaction (entries 8−12). However, no results surpassed that obtained in CH_2Cl_2.

To demonstrate the efficiency of this method, we next examined a variety of 4-(dimethoxyphosphoryl)-3-arylbut-2-enoic acid methyl esters under the optimized hydrogenation

TABLE 1. Asymmetric Hydrogenation of 3-Phenyl-4-Phosphonobutenoates 5a−5d[a]



entry	ligand	substrate (R^1, R^2)	solvent	conv. (%)[b]	ee (%)[c]
1	FAPhos	**5a** (^{i}Pr, ^{i}Pr)	CH_2Cl_2	87	25
2	WalPhos	**5a** (^{i}Pr, ^{i}Pr)	CH_2Cl_2	100	< 10
3	BoPhoz	**5a** (^{i}Pr, ^{i}Pr)	CH_2Cl_2	94	30
4	(S_c,R_p,R_{Fc})-**9a**	**5a** (^{i}Pr, ^{i}Pr)	CH_2Cl_2	100	78
5	(S_c,R_p,R_{Fc})-**9b**	**5a** (^{i}Pr, ^{i}Pr)	CH_2Cl_2	100	85
6	(S_c,R_p,R_{Fc})-**9b**	**5b** (Et, ^{i}Pr)	CH_2Cl_2	100	94
7	(S_c,R_p,R_{Fc})-**9b**	**5c** (Et, Et)	CH_2Cl_2	100	96
8	(S_c,R_p,R_{Fc})-**9b**	**5d** (Me, Me)	CH_2Cl_2	100	98
9	(S_c,R_p,R_{Fc})-**9b**	**5d** (Me, Me)	THF	100	96
10	(S_c,R_p,R_{Fc})-**9b**	**5d** (Me, Me)	toluene	80	91
11	(S_c,R_p,R_{Fc})-**9b**	**5d** (Me, Me)	MeOH	100	95
12	(S_c,R_p,R_{Fc})-**9b**	**5d** (Me, Me)	^{i}PrOH	100	95

[a]The reactions were carried out in 2 mL of solvent for 24 h under 60 bar of H_2 with 0.25 mmol of substrate. Substrate/$[Rh(COD)_2]BF_4$/ligand = 100/1/1.1. [b]Conversions were determined by GC. [c]Enantiomeric excesses were determined by HPLC on a chiral column.

TABLE 2. Asymmetric Hydrogenation of 3-Substituted 4-Phosphonobutenoates 5d−n[a]

entry	substrate (R)	yield (%)[b]	ee (%)[c]
1	(*Z*)-**5d**: R = Ph	99	98 (-)
2	(*Z*)-**5e**: R = 2-$MeOC_6H_4$	96	95 (-)
3	(*Z*)-**5f**: R = 3-$MeOC_6H_4$	97	97 (-)
4	(*Z*)-**5g**: R = 4-$MeOC_6H_4$	91	93 (-)
5	(*Z*)-**5h**: R = 4-FC_6H_4	99	95 (-)
6	(*Z*)-**5i**: R = 4-ClC_6H_4	99	96 (*S*)
7	(*Z*)-**5j**: R = 4-BrC_6H_4	98	97 (-)
8	(*Z*)-**5k**: R = 4-$NO_2C_6H_4$	92	96 (-)
9	(*Z*)-**5l**: R = 2-naphthyl	96	94 (-)
10	(*Z*)-**5m**: R = 2-thiophenyl	97	93 (-)
11	(*Z*/*E*)-**5n**: R = Me	-[d]	-[d]

[a]The reactions were carried out in 2 mL of CH_2Cl_2 for 24 h under 60 bar of H_2 with 0.25 mmol of substrate. Substrate/$[Rh(COD)_2]BF_4$/ligand = 100/1/1.1. [b]Isolated yields. [c]The ee values were determined by HPLC on a chiral column.. [d]Not determined due to low conversion

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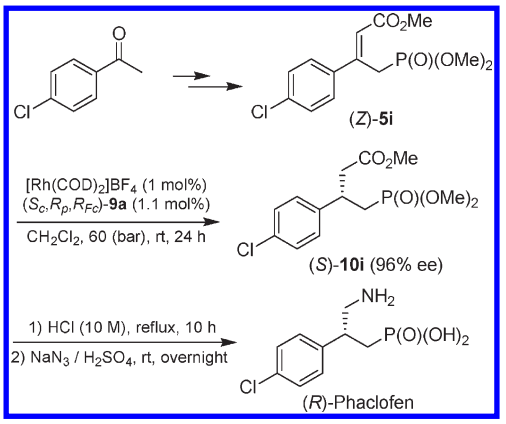
SCHEME 2. Stereoselective Synthesis of (*R*)-Phaclofen



conditions, and the results are shown in Table 2. Full conversions and good to excellent enantioselectivities were obtained for all of the substrates. The results indicated that there is only a slight influence on the substitution pattern of the substituent on the phenyl ring of substrates (entries 2−4). All three substrates with a methoxy group on the phenyl ring were hydrogenated in good enantioselectivities (93−97% ee) (entries 2−4). The electronic properties of the substituent on the 4-position of the phenyl ring of substrates also showed little effect on the enantioselectivity, all substrates with a para substituent were hydrogenated in 93−97% ee (entries 4−8). 4-(Dimethoxyphosphoryl)-3-(2-naphthyl)but-2-enoic acid methyl ester also worked well, giving an ee-value of up to 94% (entry 9). Good enantioselectivity (93% ee) was also observed in the hydrogenation of the substrate containing a thiophene-heteroaryl group (entry 10). However, low conversion was achieved in the hydrogenation of 3-alkyl-substituted substrate **5n** (entry 11).

To explore the synthetic utility of this method, we employed it as a key step in the enantioselective synthesis of (*R*)-phaclofen, a potential $GABA_B$ antagonist,[12] as shown in Scheme 2. The studies have disclosed that the $GABA_B$ receptor affinity and antagonist effect of phaclofen resides in the (*R*)-enantiomer.[13] The present method for obtaining optically active (*R*)-phaclofen involved the resolution of racemic phaclofen, and there is still no report of an asymmetric method.[14] The development of an enantioselective approach for the synthesis of (*R*)-phaclofen is therefore highly desirable. For the synthesis of (*R*)-phaclofen, (*S*)-**10i** was obtained as a key chiral intermediate in 96% ee by use of the present hydrogenation method. Hydrolysis of (*S*)-**10i** with aqueous HCl followed by treatment with NaN_3 in sulfuric acid at ambient temperature gave (*R*)-phaclofen in 61% yield.

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In summary, we have developed a highly efficient method for the enantioselective synthesis of 3-aryl-4-phosphonobutyric acid esters via the first Rh-catalyzed asymmetric hydrogenation of 3-aryl-4-phosphono-butenoate, in which 93−98% ee were achieved. This method is potentially useful for the preparation of a number of chiral pharmaceuticals such as (*R*)-phaclofen. Further investigation will be reported in due course.

Experimental Section

α,β-Unsaturated esters **3** and allylic bromides **4** were prepared according to the known methods.[7]

General Procedure for the Preparation of 3-Aryl-4-phosphonobutenoates 5. A solution of allylic bromides **4** (10 mmol) and trimethyl phosphite (3 equiv., 30 mmol) was heated to 150 °C and stirred at the same temperature for 3 h. Excess trimethyl phosphite were removed in vacuo. Flash chromatography of the residue on silica gel (AcOEt/hexane 1:1) gave pure product.

Methyl 3-(4-chlorophenyl)-4-(dimethoxyphosphoryl)but-2-enoate (5i). 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.64 (s, 3H), 3.78 (s, 3H), 3.90 (d, J = 24.4 Hz, 2H), 6.20 (d, J = 5.6 Hz, 1H), 7.35−7.37 (m, 2H), 7.46−7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6 (d, J = 134.0 Hz), 51.4, 52.7, 119.8 (d, J = 10.0 Hz), 128.2, 128.8, 135.4, 138.7, 148.3 (d, J = 11.0 Hz), 166.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.2; HRMS calcd for $C_{13}H_{16}ClO_5NaP$ [M + Na] 341.0322, found 341.0320.

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_p,R_{Fc})-**9b**. The mixture was stirred at room temperature for 15 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 a hydrogen pressure of 60 bar was maintained. The hydrogenation was performed at room temperature for 24 h. After careful release of 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.

Methyl 3-(4-chlorophenyl)-4-(dimethoxyphosphoryl)-butanoate (10i): 96% ee; $[\alpha]^{25}_D$ = −3.53 (1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07−2.22 (m, 2H), 2.61−2.67 (m, 1H), 2.86−2.91 (m, 1H), 3.52−3.61 (m, 10H), 7.17−7.19 (m, 2H), 7.27−7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2 (d, J = 139.0 Hz), 35.9, 41.3 (d, J = 11.0 Hz), 51.6, 52.1, 52.3, 128.7, 132.8, 141.4 (d, J = 9.0 Hz), 171.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.4; HRMS calcd for $C_{13}H_{18}O_5PCl$ 320.0580, found 320.0572; HPLC (Chiralpak AS-H, elute: 10% 2-propanol/90% *n*-hexane, flow rate: 1.0 mL/min, detector: 215 nm), (*S*) t_1 = 36.0 min; (*R*) t_2 = 42.6 min.

Acknowledgment. We are grateful for the generous financial support from the National Natural Science Foundation of China (20802076, 20873145, and 20972156), the Knowledge Innovation Program of the Chinese Academy of Sciences (DICP-S200802), and the Planned Science and Technology Project of Dalian (2009E11SF132).

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