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Synthesis of chiral 1,3-bis(1-(diarylphosphoryl)ethyl)-benzenes via Ir-catalyzed double asymmetric hydrogenation of bis(diarylvinylphosphine oxides)

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A class of chiral 1,3-bis(diarylphosphinoethyl)benzenes, which are key intermediates for the synthesis of PCP-type chiral pincer ligands, were prepared in high diastereomeric ratios and excellent ee values via double asymmetric hydrogenation of the corresponding bis(diarylvinylphosphine oxide) substrates using a SpinPhox/Ir(I) complex as the catalyst. The hydrogenation product **5a** was readily transformed into the corresponding borane-protected chiral PCP-type pincer ligand **7a** with high enantiomeric excess, exemplifying a viable synthetic route to optically active chiral PCP pincer ligands.

bis(diarylvinylphosphine oxide), iridium, asymmetric hydrogenation, PCP-type chiral pincer ligands

1 Introduction

Over the past several decades, transition metal complexes with PCP-type pincer ligands (Figure 1) have gained much attention because of their extensive applications in various fields of chemistry [1, 2]. The neighboring phosphine units on the pincer-type ligands can facilitate the metal insertion into the middle C–H bond, leading to the formation of robust metal complexes with well-defined structures and interesting physicochemical properties [3]. By this way, the PCP pincer ligands adopt tridentate coordination with transition metals, thus providing excellent opportunities to fine tune the metal complex properties for catalysis [4–6]. Particularly, the chiral PCP-type pincer ligands can offer a unique chiral environment and stereoelectronic features for the resident metal, and have found successful applications in a variety of catalytic asymmetric reactions in recent decades [7–18]. Despite the progress, the development of chiral PCP-type ligands is relatively slow, presumably hampered by their tedious multistep syntheses and difficulties in stereochemical manipulations. So far, chiral PCP-type ligands were usually prepared by resolution or the use of stoichiometric chiral auxiliaries. In 1994, Venanzi and coworkers [7] reported a multistep synthesis of the first optically pure PCP ligand, and the use of its platinum pincer complex in the aldol condensation of aldehydes with methyl isocyanate. In late 1990s, Zhang and coworkers [8, 9] developed a general method for the synthesis of chiral PCP-type ligands, by using (+)-DiPCl as a stoichiometric reagent in the key step of 1,3-diacetylbenzene asymmetric reduction. Kirchner and coworkers [19] reported a modular synthesis of some chiral PCP-type bis-phosphoramidite ligands containing chiral phosphite units in 2006. There have also been several recent literature reports on the catalytic asymmetric synthesis of chiral diphosphine ligands, however, the examples of PCP are only sporadical in most cases. Bergman and coworkers [20] reported a Ru-catalyzed enantioselective synthesis of P-stereogenic phosphine-boranes, with an example of a bisborane protected PCP pincer ligand being obtained in

Dedicated to Professor Qian Changtao on the occasion of his 80th birthday.
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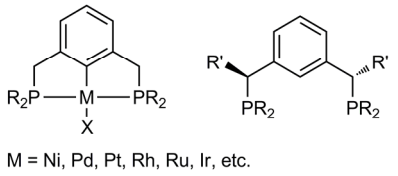


Figure 1 PCP-type pincer ligands and their metal complexes.

95% ee via asymmetric alkylation. Duan and coworkers [10, 11] reported the synthesis of a chiral PCP pincer ligand or its Pd complex via a Pd-catalyzed double asymmetric conjugate addition of diarylphosphines to a phenyl-based bisenal or bisenone compound. Leung and coworkers [21] reported a highly diastereo- and enantioselective synthesis of chiral PCP pincer ligands via Pd-catalyzed hydrophosphination of dienones with diphenylphospine. Given the significance and challenges in PCP- type chiral ligand synthesis, development of efficient, general, and enantioselective routes to these compounds are highly desirable. We envisioned that metal catalyzed double asymmetric hydrogenation (AH) [22–24] of 1,3-bis(1-(diarylphosp horyl) vinyl)benzene derivatives would provide a viable route to PCP-type chiral pincer ligands via the formation of optically active 1,3-bis(diarylphosphinoyl) benzenes, since diphosphine oxides can be used as key synthetic precursors for the diphosphine ligands [25]. In this context, Matteoli and coworkers [26] reported in 2000 the synthesis of chiraphos, a chiral chelating diphosphine ligand, via Ru-(*S*)-BINAP catalyzed asymmetric hydrogenation of 2,3-bis(diphenylphosphinoyl)buta-1,3-diene. Andersson and coworkers [27] have also disclosed a highly enantioselective synthesis of diphenylphosphine oxides via chiral N,P-Ir catalyzed asymmetric hydrogenation [28–38]. We have previously reported the use of SpinPHOX/Ir^{I} catalysts **1**, for efficient asymmetric hydrogenation of ketimines [39], α,β-unsaturated carboxylic acids [40], α,β-unsaturated Weinreb amides [41], α,α′-bis(2-hydroxyarylidene)ketones [42, 43], as well as a range of cyclic α-alkylidene carbonyl compounds [44]. Herein, we report the first application of SpinPHOX/Ir^{I} catalysts in the asymmetric hydrogenation of the challenging 1,3-bis(1-(diarylphosphoryl)vinyl)benzene derivatives, giving 1,3-bis(diarylphosphinoyl)benzenes in high diastereomeric ratios and excellent ee values. The synthetic utility of the procedure was exemplified by the ready conversion of a hydrogenation product into the corresponding enantiopure borane-protected chiral PCP-type pincer ligand.

2 Experimental

2.1 General information

Unless otherwise noted, all reactions and manipulations involving air- or moisture-sensitive compounds were performed using standard Schlenk techniques or in a glovebox. All solvents were purified and dried using standard procedures. Melting points were measured on a RY-I apparatus and uncorrected. ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectra were recorded on Varian Mercury 300 or 400 MHz spectrometers. Chemical shifts (δ values) were reported in ppm downfield from internal TMS (^{1}H NMR), $CDCl_3$ (^{13}C NMR), external 85% H_3PO_4 (^{31}P NMR), and external CF_3CO_2H (^{19}F NMR), respectively. Optical rotations were determined using a Perkin Elmer 341 MC polarimeter. The IR spectra were measured on a BRUKER TENSOR 27 FT-IR spectrometer. EI-MS (70 eV) and ESI-MS spectra were obtained on an Agilent 5973N or a Shimadzu LCMS-2010EV spectrometer, respectively. HRMS (EI), HRMS (ESI), and HRMS (MALDI/DHB) were determined on Bruker APEXIII 7.0 TESLA FT-MS, Agilent Technologies 6224 TOF LC/MS, or IonSpect 4.7 TESLA FTMS spectrometers, respectively. HPLC analyses were performed on a JASCO 2089 liquid chromatograph.

2.2 Synthesis of the SpinPHOX/Ir^{I} complexes (*R*,*S*)-1a–e and (*S*,*S*)-1a–d

The Ir complexes (*R*,*S*)-**1a–e** and (*S*,*S*)-**1a–d** (Figure 2), for the asymmetric hydrogenation reactions were synthesized by following our previously reported procedures [39].

2.3 General procedure for the synthesis of 1,3-bis(1-(diarylphosphoryl)vinyl)benzenes 4a–i

A reaction tube under argon atmosphere was charged with diphenylphosphine oxide (5.2 mmol), $Pd(OAc)_2$ (0.25 mmol), 1,2-bis(diphenylphosphino)ethane (dppe, 0.375 mmol), 1,3-diethynyl-5-substituented benzene (2.6 mmol) and chlorobenzene (20 mL). The mixture was heated at 130 °C for 10 h. The reaction mixture was allowed to cool to room temperature, and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (60:1–20:1, *v*/*v*) as the eluents.

The characterization of compounds **4a–i** were shown in the Supporting Information online.

2.4 General procedure for asymmetric hydrogenation of the 1,3-bis(1-(diarylphosphoryl)vinyl)benzene substrates 4a–i

To a vial containing CH_2Cl_2 (1.5 mL) and a magnetic stirring bar were added the SpinPHOX/Ir precatalyst (*R*,*S*)-**1** or

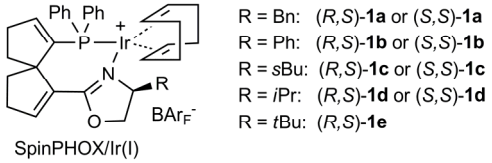


Figure 2 SpinPHOX/Ir^{I} catalysts (*R*,*S*)-**1a–e** and (*S*,*S*)-**1a–d**.

(*S*,*S*)-**1** (0.015 mmol) and the substrate **4** (0.15 mmol) under an argon atmosphere. The vial was transferred in a glove box to a Parr steel autoclave, which was purged three times with hydrogen and finally pressurized to the specified pressure. The reaction mixture was stirred at 50 °C for 20 h. The residual hydrogen gas was released in a hood, and the conversion was determined by ^{1}H NMR analysis of an aliquot of the crude mixture. The reaction mixture was filtered through a short pad of silica gel, and the solvent of the filtrate was removed in vacuo to afford the product. The diastereomeric ratios (*dr* = *dl*/*meso*) and ee values of the double asymmetric hydrogenation products **5a–i** were determined by chiral HPLC, while the ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR, and FT-IR spectral data were recorded on diastereomeric (*racemic*/*meso*) **5a–i** obtained by Pd/C catalyzed hydrogenation of **4a–i**, respectively.

The characterization of compounds **5a–i** were shown in the Supporting Information online.

2.5 Procedure for the synthesis of [(1*R*,1′*R*)-1,3-bis[1-(diphenylphosphino)ethyl]benzene]-bisborane 7

A reaction tube under nitrogen atmosphere was charged with 1,3-bis(1-(diphenylphosphoryl)ethyl)benzene **5a** (270 mg, 0.5 mmol), Ti(O^{i}Pr)$_4$ (0.05 mL, 0.1 mmol), tetramethyldisilazane (TMDS, 0.7 mL, 3.5 mmol), and toluene (10 mL). The reaction mixture was heated at 80 °C for 12 h, then allowed to cool to room temperature. A solution of BH_3/THF (1.0 mol/L, 1.3 mL, 1.3 mmol) was added, and the resulting mixture was stirred further for 12 h. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel with EtOAc/hexane (1:10, *v*/*v*) as the eluent to afford [(1*R*,1′*R*)-1,3-bis[1-(diphenylphosphino)ethyl]benzene]-bisborane **7** as a white solid. Yield: 95%; m.p. 155–156 °C (lit. m.p. 157–159 °C) [9], 99% ee, 91:9 *dr*, $[\alpha]_D^{20}$ = +189.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.82 (m, 4H), 7.54–7.47 (m, 6H), 7.34–7.30 (m, 6H), 7.23–7.19 (m, 4H), 7.00 (s, br, 1H), 6.89 (s, br, 3H), 3.72–3.63 (m, 2H), 1.48 (dd, J_{P-H} = 16.0 Hz, J_{H-H} = 7.2 Hz, 6H) ppm. The enantiomeric excess and diatereomeric ratio were determined by HPLC on Chiralcel ID-3 column, hexane:isopropanol = 80:20, flow rate = 0.7 mL/min, UV detection at λ = 230 nm, t_R = 14.5 min (major), t_R = 17.0 min (*meso*), t_R = 33.2 min (minor). The diastereomeric mixture was further purified by recrystallization from ethyl acetate/petroleum ether to give (1*R*,1′*R*)-**7** as a single isomer (> 99% ee).

3 Results and discussion

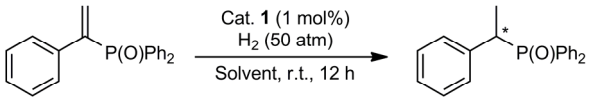
3.1 SpinPHOX/Ir^I catalyzed asymmetric hydrogenation of diphenyl(1-phenylvinyl)phosphine oxide 2

The initial test for the viability of the catalysis was performed using AH of diphenyl(1-phenylvinyl)phosphine oxide **2** as the model reaction [27] and 1.0 mol% of (*R*,*S*)- or (*S*,*S*)-**1** as the catalyst. The reactions were conducted under 50 atm of H_2 at room temperature for 12 h, and the results are shown in Table 1. For the reactions performed in dichloromethane, large variations were observed in both the catalytic activity (39%–>99% conversions) and the enantioselectivity (19%–91% ee), depending on the (*R*,*S*)- or (*S*,*S*)-configu- rations and the oxazolyl substituent of the catalyst (entries 1–9). Under these conditions, catalysts (*R*,*S*)-**1b** and (*S*,*S*)-**1b**, both bearing a Ph group on the (*S*)-oxa-zolyl moiety, turned out to be optimal for the reaction in terms of both enantiocontrol and reactivity, both resulting in full substrate conversions to afford the hydrogenation product **3** with 91% *ee* albeit in opposite absolute configuration (entries 2 and 7). Further screening of the reaction conditions using catalyst (*R*,*S*)-**1b** revealed a profound solvent effect, as the AH of **2** in several other types of solvents all gave results inferior to those in dichloromethane (entries 10–14 vs 2).

3.2 Substrate synthesis and initial test for double asymmetric hydrogenation of 1,3-bis(1-(diphenylphosphoryl)vinyl)benzene

Encouraged by the excellent preliminary results attained in the hydrogenation of **2** with catalysts (*R*,*S*)- and (*S*,*S*)-**1b**, we sought to extend this procedure to the AH of 1,3-bis(1-(diphenylphosphoryl)vinyl)benzenes **4**, a type of bisolefins with two (diphenylphosphoryl)vinyl units on the *meta*-positions of a phenyl backbone. Pd/CuI catalyzed Sonogashira

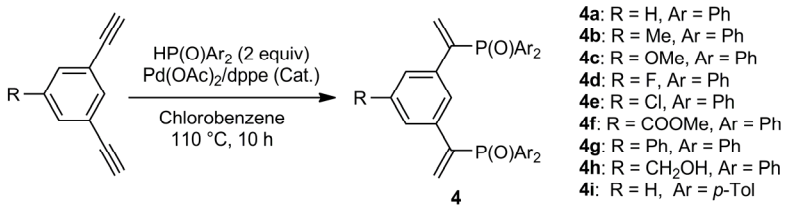
Table 1 SpinPHOX/Ir^I (**1**) catalyzed AH of diphenylvinylphosphine oxide **2** [a]



2 **3**

Entry	Cat.	Solvent	Conv. (%) [b]	ee (%) [c]
1	(*R*,*S*)-**1a**	CH_2Cl_2	> 99	88 (*R*)
2	(*R*,*S*)-**1b**	CH_2Cl_2	> 99	91 (*R*)
3	(*R*,*S*)-**1c**	CH_2Cl_2	> 99	71 (*R*)
4	(*R*,*S*)-**1d**	CH_2Cl_2	> 99	83 (*S*)
5	(*R*,*S*)-**1e**	CH_2Cl_2	> 99	88 (*R*)
6	(*S*,*S*)-**1a**	CH_2Cl_2	72	67 (*S*)
7	(*S*,*S*)-**1b**	CH_2Cl_2	> 99	91 (*S*)
8	(*S*,*S*)-**1c**	CH_2Cl_2	43	19 (*S*)
9	(*S*,*S*)-**1e**	CH_2Cl_2	39	49 (*S*)
10	(*R*,*S*)-**1b**	DCE	74	88 (*R*)
11	(*R*,*S*)-**1b**	$CHCl_3$	71	87 (*R*)
12	(*R*,*S*)-**1b**	toluene	> 99	80 (*R*)
13	(*R*,*S*)-**1b**	THF	> 99	75 (*R*)
14	(*R*,*S*)-**1b**	MeOH	22	–

a) Unless otherwise noted, all reactions were conducted under 50 atm of H_2 at 25 °C for 12 h with [**2**] = 0.1 mol/L and [**1**] = 1 mmol/L (1 mol%); b) determined by ^{1}H NMR spectroscopy; c) determined by HPLC, and the absolute configurations were assigned by comparing their specific rotations with the literature reported values [27].

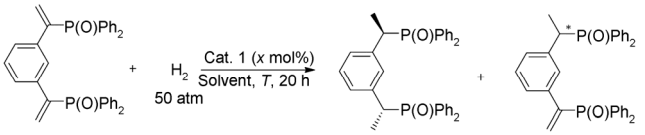


Scheme 1 Synthesis of 1,3-bis(1-(diarylphosphoryl)vinyl)benzene substrates **4a–i**.

cross-coupling of 1,3-dibromo-5-substituented benzenes with two equivalents of ethynyltrimethylsilane, followed by desilylation of the resulting 1,3-bis ((trimethylsilyl)ethynyl) substituted benzenes with aqueous potassium carbonate, readily afforded the 1,3-diethynyl-5-substituted benzenes in good overall yields (Supporting Information). Pd/dppe catalyzed regioselective double Markovnikov addition of diphenylphosphine oxide to the *meta*-diethynylbenzenes [45] proceeded smoothly in refluxing chlorobenzene, giving the 1,3-bis(1-(diarylphosphoryl) vinyl)benzene substrates **4a–i** in moderate to high yields (Scheme 1).

Subsequent efforts were made to extend the AH protocol to 1,3-bis(1-(diphenylphosphoryl)vinyl)benzene **4a** using either (*R*,*S*)- or (*R*,*S*)-**1b** as the catalyst (Table 2). The reaction under the conditions optimized for diphenylvinylphosphine oxide **2** using 2.0 mol% of (*R*,*S*)-**1b** as the catalyst, however, only resulted in partial conversion (50%) of the substrate to give compound **5a** as a minor product, along with a substantial amount of the mono-hydrogenated product **6** (entry 1). This observation suggested that the double asymmetric hydrogenation of **4a** to **5a** is most likely to proceed in a stepwise fashion via the formation of **6** as the intermediate. Even worse results were obtained using catalyst (*S*,*S*)-**1b** under otherwise identical conditions (entry 2), suggesting that the catalyst might be deactivated to some extent by the weak coordination of the hydrogenation product, and that a higher catalyst loading and/or more forcing conditions should be resorted for double AH of **4a**. Indeed, increasing the catalyst loading of (*R*,*S*)-**1b** to 5.0 mol% while gradually elevating the temperature to 50 °C, led finally to a full conversion of **4a** and disappearance of **6** (entries 3–5). In the last case, the double AH product **5a** was obtained quantitatively with an excellent enantiopurity (96% ee), but the diastereomeric ratio (*dl*/*meso*) was only moderate (70:30, entry 5). Changing the reaction medium to toluene gave rise to essentially comparable catalytic performance as that in dichloromethane (entry 6 vs 5). Gratifyingly, further increment of the catalyst loading of (*R*,*S*)-**1b** to 10 mol% afforded complete conversion to (*R*,*R*)-**5a** with excellent ee (98%) and good *dr* (85:15) values (entry 7). It is also interesting to note that catalyst (*S*,*S*)-**1b** afforded (*S*,*S*)-**5a** in good *dr* (87:13) and 97% ee under otherwise identical conditions, demonstrating asymmetric induction complementary to (*R*,*S*)-**1b** in the double AH of **4a**.

Table 2 **1b**-Catalyzed AH of 1,3-bis(1-(diphenylphosphoryl)vinyl) benzene **4a** [a]



Entry	Cat. (*x* mol%)	*T* (°C)	Conv. (%) [b]	**5a**:**6** [b]	ee (%) [c]	*dr* (%) [c]
1	(*R*,*S*)-**1b** (2)	25	50	1:2.9	N.D. [e]	N.D.
2	(*S*,*S*)-**1b** (2)	25	trace	N.D.	N.D.	N.D.
3	(*R*,*S*)-**1b** (5)	25	74	1:1.6	N.D.	N.D.
4	(*R*,*S*)-**1b** (5)	40	80	1:1.5	N.D.	N.D.
5	(*R*,*S*)-**1b** (5)	50	> 99	1:0	96 (*R*,*R*)	70:30
6 [d]	(*R*,*S*)-**1b** (5)	50	> 99	1:0	96 (*R*,*R*)	66:34
7	(*R*,*S*)-**1b** (10)	50	> 99	1:0	98 (*R*,*R*)	85:15
8	(*S*,*S*)-**1b** (10)	50	> 99	1:0	97 (*S*,*S*)	83:17

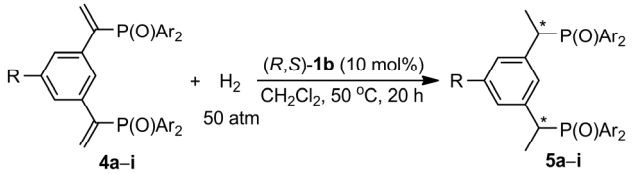
a) Unless otherwise specified, the reactions were conducted in dichloromethane in a Parr autoclave under 50 atm of H_2 for 20 h with [**4a**] = 0.1 mol/L; b) determined by ^{1}H NMR spectroscopy; c) the *dr* (*dl*/*meso*) and ee values of **5a** were determined by chiral HPLC, and the absolute configuration of chiral **5a** was deduced to be (*R*,*R*) by comparing the optical rotation with that of its borane protected reduction derivative (1*R*,1′*R*)-**7** (vide infra); d) the reaction was conducted in toluene; e) N.D. represents not determined.

3.3 AH of 1,3-bis(1-(diarylphosphoryl)vinyl)benzenes and the synthesis of a PCP-type chiral pincer ligand

Under the optimized conditions, the double AH protocol was successfully extended to a number of 5-substituted 1,3-bis(1-(diarylphosphoryl)vinyl)benzene derivatives **4a–i**. As shown in Table 3, in each case the reaction proceeded smoothly under the catalysis of (*R*,*S*)-**1b**, to afford the corresponding chiral bisphosphine oxides **5a–i** in high *dl*/*meso* ratios (*dr* 85:15–98:2). The enantioselectivities for **5a–i** are uniformly excellent (91%–99% ee), irrespective of the electron-donating (entries 2 and 3) or -withdrawing (entries 4–6) nature of the 5-substituent on the phenyl backbone. It is noteworthy that apart from the methoxy (entry 3), fluoro (entry 4), and carbomethoxy (entry 6) groups, the reaction with substrate **4h** bearing a free 5-hydroxymethyl group also proceeded well with good *dr* and excellent ee values (entry 8), suggesting a high functional group tolerance of the double AH protocol.

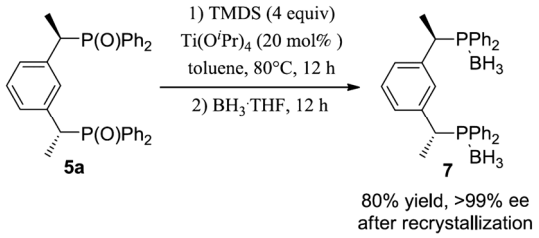
To demonstrate the synthetic utility of the present procedure, the product (+)-**5a** was reduced to the corresponding

Table 3 **1b**-Catalyzed AH of 1,3-bis(1-(diarylphosphoryl)vinyl)benzenes **4a–i** [a]



Entry	Substrate	R	Ar	ee (%) [b]	*dr* (%) [b]
1	**4a**	H	Ph	98 (+)	85:15
2	**4b**	Me	Ph	98 (+)	92:8
3	**4c**	OMe	Ph	98 (+)	85:15
4	**4d**	F	Ph	98 (+)	86:14
5	**4e**	Cl	Ph	99 (+)	90:10
6	**4f**	COOMe	Ph	98 (+)	90:10
7	**4g**	Ph	Ph	95 (+)	93:7
8	**4h**	CH_2OH	Ph	91 (+)	93:7
9	**4i**	H	*p*-Tol	99 (+)	98:2

a) The reactions were performed in a Parr autoclave under 50 atm of H_2 with 0.15 mmol of **4a–i** in CH_2Cl_2 (1.5 mL) in the presence of 10 mol% of (*R*,*S*)-**1b** at 50 °C, and the conversion in each case was determined to be > 99% by ^{1}H NMR analysis; b) the *dr* and ee values of **5a–i** were determined by chiral HPLC.



Scheme 2 Conversion of **5a** to the bisborane-protected chiral PCP-type pincer ligand (*R*,*R*)-**7**.

bisphosphine by treatment with TMDS in THF, which upon *in situ* borylation with BH_3·THF gave the corresponding air-stable bisborane-protected chiral PCP-type pincer ligand (*R*,*R*)-**7** in 99% ee with 9% *meso* isomer (Scheme 2). Purification of **7** by recrystallization from ethyl acetate/petroleum ether gave a single optically pure (*R*,*R*)-enantiomer, which would allow for a facile access to the corresponding chiral PCP ligand after borane deprotection [9].

4 Conclusions

In summary, we have developed an efficient procedure for the synthesis of chiral 1,3-bis(diarylphosphinoethyl)benzenes, via double asymmetric hydrogenation of 1,3-bis(1-(diarylphosphoryl)vinyl)benzenes using the Ir(I) complexes **1** as catalysts. Good to high diastereomeric ratios (up to 98:2) and excellent ee values (91%–99%) were achieved for the resulting chiral bisphosphine oxides, which can be readily transformed into the corresponding chiral PCP-type pincer ligands via simple synthetic manipulations. Further studies on extension of the procedure to the synthesis of chiral PCP-ligands and their applications in asymmetric catalytic reactions are underway.

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