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DESIGN AND SYNTHESIS OF A C_2-SYMMETRIC CHIRAL 1,2-BIS(DIPHENYLPHOSPHINO)BENZENE LIGAND VIA RHODIUM-CATALYZED INTRAMOLECULAR [2+2+2] CYCLOADDITION

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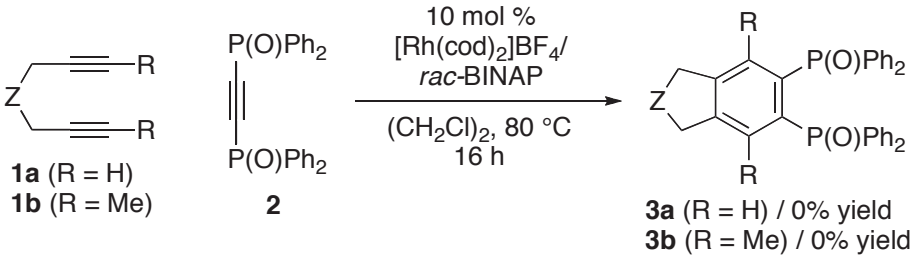
Abstract – The design and synthesis of a C_2-symmetric chiral 1,2-bis(diphenylphosphino)benzene ligand via the rhodium-catalyzed intramolecular [2+2+2] cycloaddition followed by reduction are disclosed. This new chiral dppbz-type ligand could be employed for the rhodium-catalyzed asymmetric alkene hydrogenation.

1,2-Bis(diphenylphosphino)benzene (dppbz) has been widely employed as a useful ligand for a number of transition-metal-catalyzed reactions.[1] As dppbz is an achiral ligand, asymmetric variants of transition-metal-catalyzed reactions, in which the dppbz ligand is indispensable, cannot be developed. Therefore, the design and synthesis of chiral dppbz-type ligands are important subjects.[2] On the other hand, the cationic rhodium(I)/biaryl bisphosphine complex-catalyzed [2+2+2] cycloadditions[3–5] involving phosphorus-substituted alkynes are useful methods for the synthesis of phosphorus-substituted benzenes.[6,7] In order to synthesize dppbz-type ligands, we attempted the reactions of terminal and internal 1,6-diynes **1a**,**b** with bis(diphenylphosphinoyl)acetylene (**2**) in the presence of a cationic rhodium(I)/*rac*-BINAP complex (10 mol %), while the expected 1,2-bis(diphenylphosphinoyl)benzenes **3a**,**b** were not obtained at all even at the elevated temperature (80 °C) (Scheme 1).

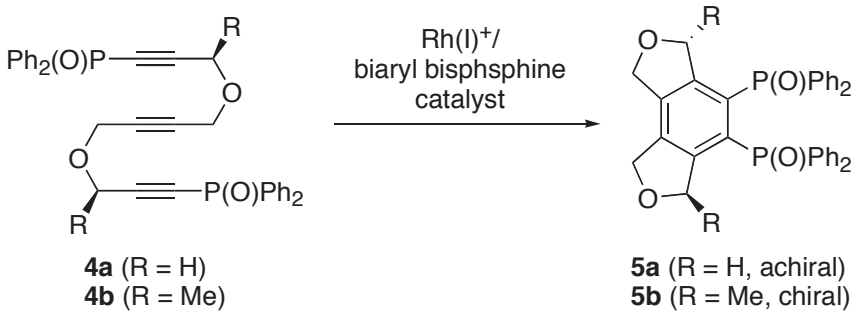
Thus, we designed the intramolecular [2+2+2] cycloaddition of triyne diphosphine oxide **4a**, which would furnish tricyclic 1,2-bis(diphenylphosphinoyl)benzene **5a** (Scheme 2). In this reaction, the use of chiral propargyl alcohol-derived triyne diphosphine oxide **4b** would furnish C_2-symmetric chiral tricyclic

Dedicated to Professor Dr. Ei-ichi Negishi on the occasion of his 77th birthday.

1,2-bis(diphenylphosphinoyl)benzene **5b** (Scheme 2). In this Communication, we disclose the synthesis of a new chiral 1,2-bis(diphenylphosphino)benzene ligand as well as achiral one via the rhodium-catalyzed intramolecular [2+2+2] cycloaddition.

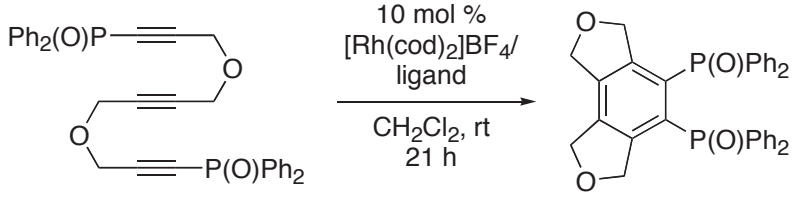


Scheme 1. Rhodium-Catalyzed Reactions of 1,6-Diynes **1** with Bis(diphenylphosphinoyl)acetylene (**2**)



Scheme 2. Rhodium-Catalyzed [2+2+2] Cycloadditions of Triyne Diphosphine Oxides **4**

Table 1. Optimization of Reaction Conditions for Rhodium-Catalyzed Intramolecular [2+2+2] Cycoaddition of Triyne **4a**[a]



entry	ligand	conv (%)[b]	yield (%)[c]
1[d]	BIPHEP	100	80
2	BINAP	100	94
3	H_8-BINAP	100	93
4	Segphos	100	91

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), ligand (0.010 mmol), **4a** (0.10 mmol), and solvent (2.0 mL) were used. [b] Determined by ^1H NMR. [c] Isolated yield. [d] For 25 h.

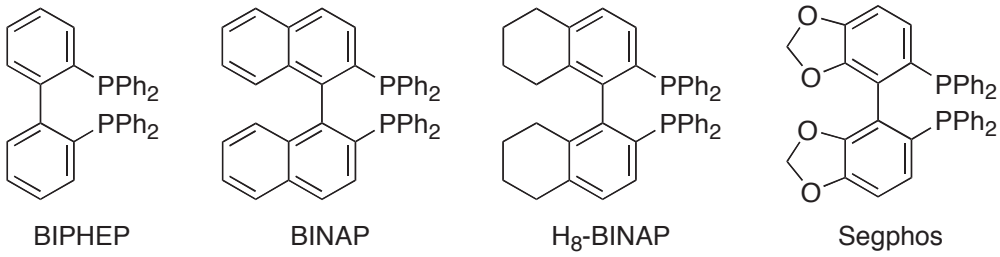
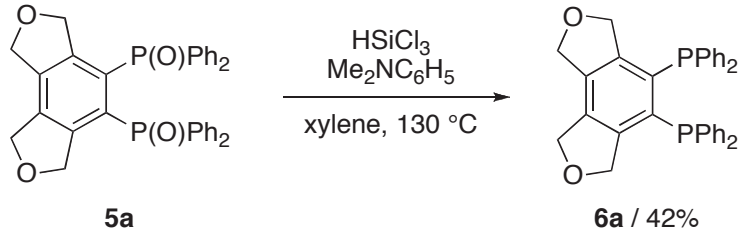


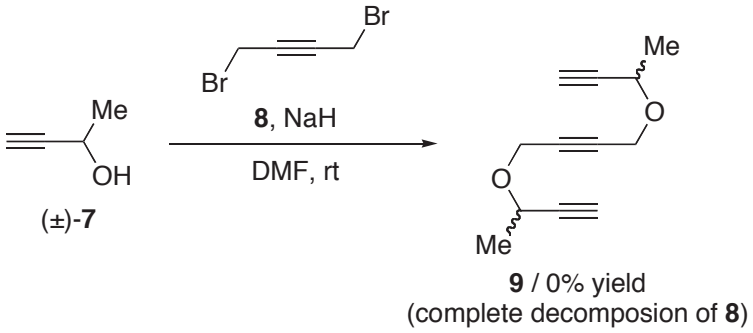
Figure 1. Structures of Biaryl Bisphosphine Ligands

We first investigated the [2+2+2] cycloaddition of achiral triyne **4a** (Table 1). Pleasingly, the desired benzene **5a** was obtained in good yield at room temperature by using a cationic rhodium(I)/BIPHEP complex (entry 1). Screening of biaryl bisphosphine ligands (Figure 1, entries 1–4) revealed that the use of BINAP furnished **5a** in the highest yield (entry 2). Thus obtained diphosphine oxide **5a** was reduced to the corresponding diphosphine ligand **6a** in moderate yield by treatment with $HSiCl_3$ and $Me_2NC_6H_5$ (Scheme 3).



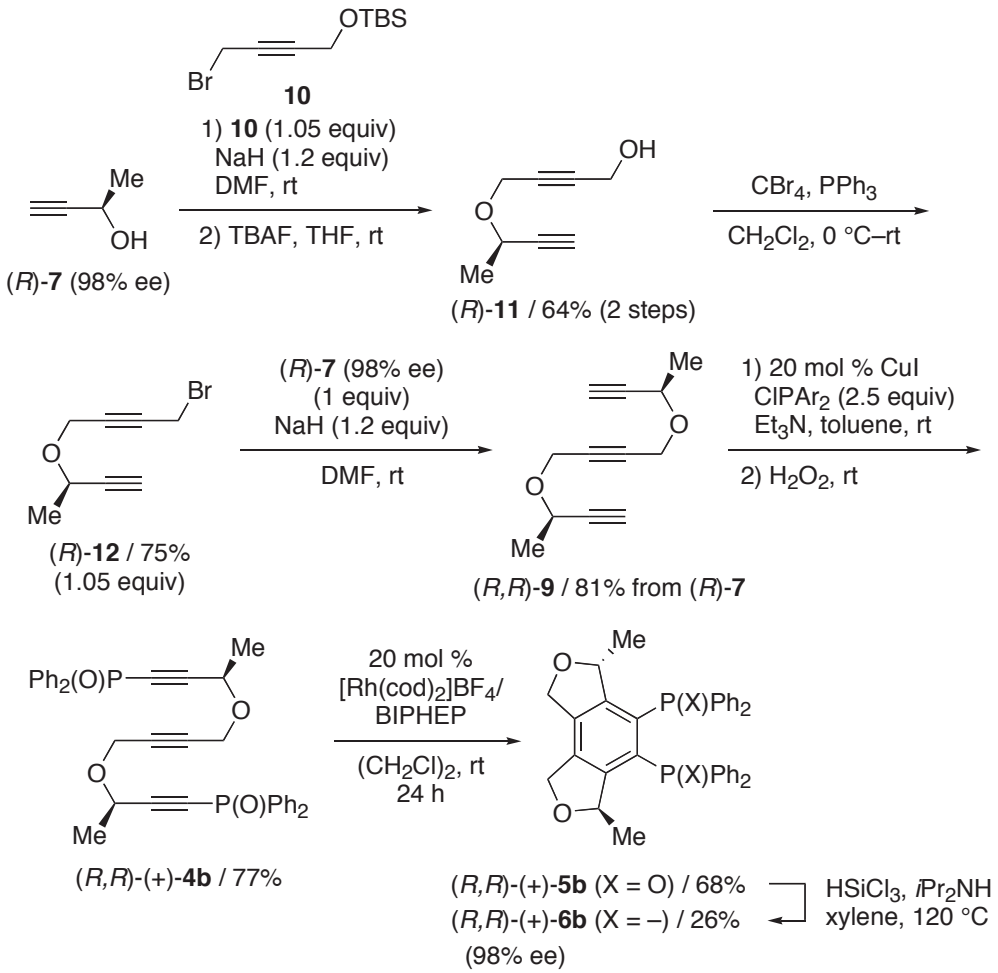
Scheme 3. Reduction of Diphosphine Oxide **5a** into Diphosphine **6a**

Next, we examined the synthesis of chiral triyne diphosphine oxide **4b** starting from commercially available chiral propargylic alcohol (*R*)-**7**. Although the double etherification of dibromide **8** with racemic (±)-**7** leading to triyne **9** was first examined, complete decomposion of **8** was observed (Scheme 4).



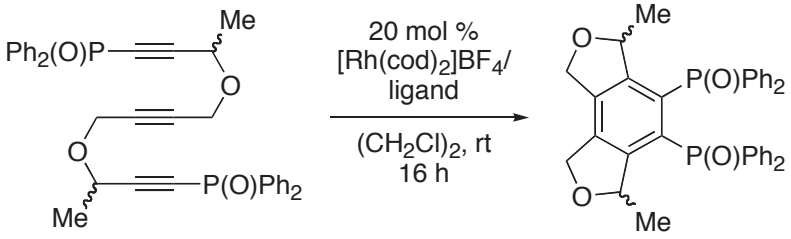
Scheme 4. Reaction of Propargylic Alcohol (±)-**7** with Dibromide **8**

Therefore, the stepwise etherification was examined as shown in Scheme 5. The etherification of bromide **10**[8] with (*R*)-**7** (98% ee) followed by desilylation afforded diyne (*R*)-**11** in good yield. Bromination of (*R*)-**11** furnished bromide (*R*)-**12** in good yield. The second etherification of (*R*)-**12** with (*R*)-**7** also proceeded to give the desired triyne (*R,R*)-**9** in high yield. The subsequent copper(I)-catalyzed double diphenylphosphination[9] followed by oxidation with H_2O_2 furnished chiral triyne diphosphine oxide (*R,R*)-(+)-**4b** in high yield. In order to optimize the [2+2+2] cycloaddition step, the reaction of diastereomeric mixture of triyne **4b**, prepared from racemic propargylic alcohol (±)-**7**, was examined by using various biaryl bisphosphine ligands (Table 2). Among the ligands examined (Figure 1, entries 1–4), the use of BIPHEP furnished the desired benzene **5b** with the highest selectivity at room temperature for 16 h, although **4b** was still remained in 24% (entry 1). Pleasingly, when the reaction of chiral triyne (*R,R*)-(+)-**4b** was conducted at room temperature for 24 h, complete conversion of **4b** was observed to give (*R,R*)-(+)-**5b** in good yield (Scheme 5). Thus obtained diphosphine oxide (*R,R*)-(+)-**5b** could be reduced to the corresponding diphosphine (*R,R*)-(+)-**6b** (98% ee) by treatment with $HSiCl_3$ and iPr_2NH, although the product yield was low.



Scheme 5. Synthesis of C_2-Symmetric Chiral 1,2-Bis(diphenylphosphino)benzene Ligand (*R,R*)-(+)-**6b** Starting from Commercially Available Chiral Propargylic Alcohol (*R*)-**7**

Table 2. Optimization of Reaction Conditions for Rhodium-Catalyzed Intramolecular [2+2+2] Cycoaddition of Triyne **4b**[a]



4b **5b** (d.r. = 1:1)

entry	ligand	conv (%)[b]	yield (%)[c]
1	BIPHEP	76	55
2	Segphos	71	32
3	BINAP	100	22
4	H_8-BINAP	15	0

[a] $[Rh(cod)_2]BF_4$ (0.0060 mmol), ligand (0.0060 mmol), **4b** (0.030 mmol), and $(CH_2Cl)_2$ (2.0 mL) were used. [b] Determined by ^1H NMR. [c] Isolated yield.

The ORTEP diagrams of [Rh(cod)((+)-**6b**)]SbF_6 are shown in Figure 2.[10] In the front view, four phenyl groups on the phosphorus atoms are distorted C_2-symmetrically due to steric repulsions between the methyl and phenyl groups. However, in the side view, four phenyl groups on the phosphorus atoms are not distorted presumably due to the high rigidity of the ligand backbone.

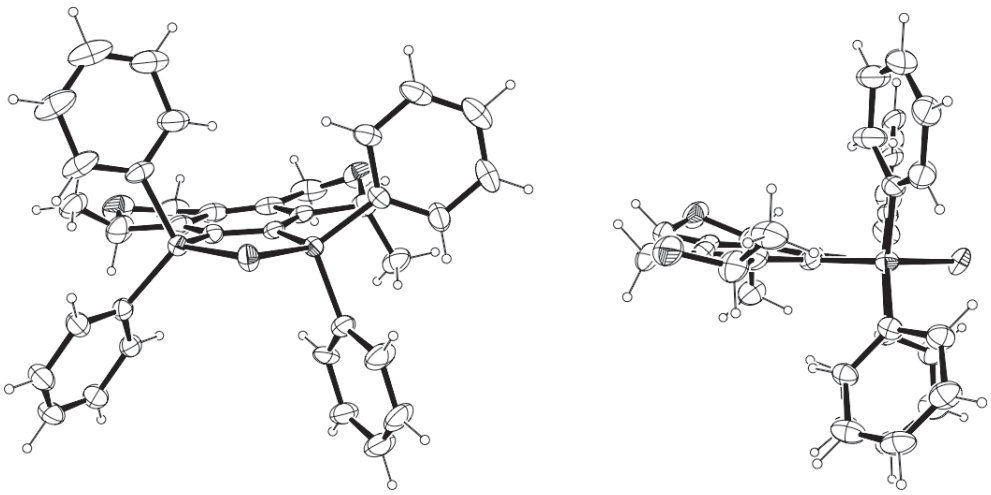
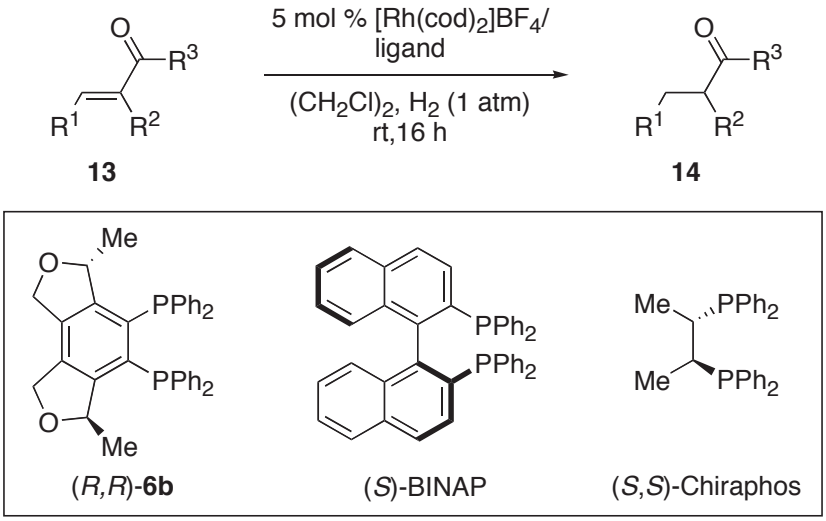


Figure 2. ORTEP diagram of [Rh(cod)((+)-**6b**)]SbF_6 with ellipsoids at 20% probability (left: front view, right: side view): cod and SbF_6 anion are omitted for clarity.

In order to evaluate a potential applicability of the chiral diphosphine ligand (*R*,*R*)-**6b** (98% ee), its application to the rhodium-catalyzed asymmetric hydrogenation of alkenes was examined briefly (Table

3). For comparison purpose, the same reactions were conducted using (*S*)-BINAP and (*S*,*S*)-Chiraphos, possessing the distorted backbone, as a ligand under the same reaction conditions. In the hydrogenation of sterically less demanding α-substituted acrylates **13a**,**b**, the ee values using (*R*,*R*)-**6b** (entries 1 and 4) were significantly lower than those using (*S*)-BINAP[7d] and (*S*,*S*)-Chiraphos (entries 2, 3, 5, and 6). On the contrary, in the hydrogenation of sterically demanding α,β-disubstituted acrylamide **13c**, the conversion and/or ee value using (*R*,*R*)-**6b** (entry 7) were markedly higher than those using (*S*)-BINAP and (*S*,*S*)-Chiraphos (entries 8 and 9). Although there remains room for improvement in the enantioselectivity, these results would demonstrate the potential utility of the new C_2-symmetric chiral dppbz-type ligand for asymmetric catalyses.

Table 3. Rhodium-Catalyzed Asymmetric Hydrogenation of Alkenes **13a–c** Using (*R*,*R*)-**6b**, (*S*)-BINAP, and (*S*,*S*)-Chiraphos[a]



entry	**13**	R^1	R^2	R^3	ligand	conv (%)[b]	**14** / ee (%)
1	**13a**	H	NHAc	OMe	(*R*,*R*)-**6b**[c]	100	(*R*)-**14a** / 7
2	**13a**	H	NHAc	OMe	(*S*)-BINAP	100	(*R*)-**14a** / 25[d]
3	**13a**	H	NHAc	OMe	(*S*,*S*)-Chiraphos	100	(*R*)-**14a** / 82
4	**13b**	H	CH_2CO_2Me	OMe	(*R*,*R*)-**6b**[c]	100	(*R*)-**14b** / 32
5	**13b**	H	CH_2CO_2Me	OMe	(*S*)-BINAP	100	(*S*)-**14b** / 76[d]
6	**13b**	H	CH_2CO_2Me	OMe	(*S*,*S*)-Chiraphos	100	(*S*)-**14b** / 82
7	**13c**	Me	Me	NPh_2	(*R*,*R*)-**6b**[c]	100	(–)-**14c** / 52
8	**13c**	Me	Me	NPh_2	(*S*)-BINAP	62	(+)-**14c** / 29
9	**13c**	Me	Me	NPh_2	(*S*,*S*)-Chiraphos	100	(+)-**14c** / 9

[a] $[Rh(nbd)_2]BF_4$ (0.0033 mmol), ligand (0.0033 mmol), **13a–c** (0.065 mmol), and $(CH_2Cl)_2$ (1.0 mL) were used. [b] Determined by ^{1}H NMR. [c] 98% ee. [d] Data reported in reference 7d.

In conclusion, we have disclosed the design and synthesis of a C_2-symmetric chiral 1,2-bis(diphenylphosphino)benzene ligand via the rhodium-catalyzed intramolecular [2+2+2] cycloaddition. This new chiral dppbz-type ligand could be employed for the rhodium-catalyzed asymmetric alkene hydrogenation. Future work will focus on further tuning of chiral ligand structures and their application to asymmetric catalyses.

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