Asymmetric Catalysis

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Enantioselective Synthesis of P-Stereogenic Alkynylphosphine Oxides by Rh-Catalyzed [2+2+2] Cycloaddition**

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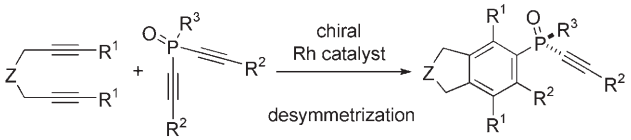
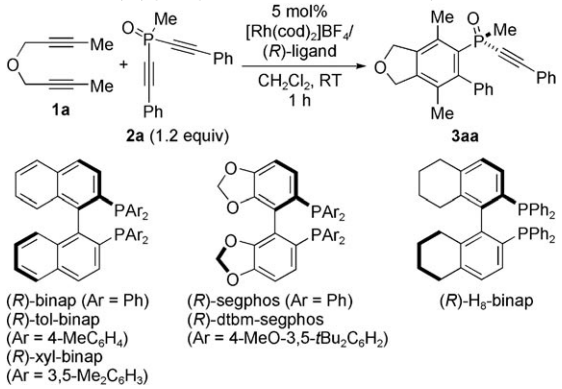
Transition-metal-catalyzed enantioselective [2+2+2] cycloadditions have been shown to be a powerful tool for the synthesis of chiral aromatic compounds.[1–5] A cationic rhodium(I)/modified-binap complex having high catalytic activity for [2+2+2] cycloadditions was first reported by our group in 2003,[6] and it is one of the most widely employed catalysts for the cycloaddition chemistry.[7] Recently, we reported that alkynylphosphine oxides are highly reactive substrates for the cationic rhodium(I)/H_8-binap complex catalyzed [2+2+2] cycloaddition; specifically, axially chiral biarylphosphine oxides were successfully synthesized through the enantioselective [2+2+2] cycloaddition of 1,6-diynes with alkynylphosphine oxides bearing a 2-alkoxynaphthyl group at the alkyne terminus with excellent yields and enantioselectivities.[8–10] Not only axially chiral biarylphosphine ligands, but also P-stereogenic phosphine ligands have been employed for a wide variety of transition-metal-catalyzed asymmetric reactions.[11] Several research groups reported the efficient asymmetric synthesis of P-stereogenic phosphorus compounds[12] by resolution[13] (including dynamic resolution[13a–c]), desymmetrization,[14] and catalytic asymmetric reactions.[15] Recently, Imamoto et al. demonstrated that P-stereogenic phosphine ligands bearing alkynyl groups induced excellent enantioselectivity in various transition-metal-catalyzed asymmetric reactions.[16] We anticipated that if selective mono [2+2+2] cycloaddition of symmetrical dialkynylphosphine oxides with 1,6-diynes proceeds by using cationic rhodium(I) complexes with modified 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl (binap) ligands as a catalyst, then P-stereogenic alkynylphosphine oxides could be accessed by desymmetrization (Scheme 1).[17]



Scheme 1. Rh-catalyzed enantioselective desymmetrization of symmetrical dialkynylphosphine oxides.

We first investigated the reaction of symmetrical dialkynylphosphine oxide **2a** and ether-linked 1,6-diyne **1a** (1.2 equiv) in the presence of the cationic rhodium(I)/(*R*)-H_8-binap complex (10 mol%). Although the reaction furnished the desired mono [2+2+2] cycloaddition product ((+)-**3aa**) in excellent yield, the enantioselectivity was moderate (Table 1, entry 1). To improve the enantioselectivity, various

Table 1: Screening of ligands for Rh-catalyzed desymmetrization of symmetrical dialkynylphosphine oxide **2a** with 1,6-diyne **1a**.[a]



No.	Ligand	Yield [%][b]	*ee* [%]
1	(*R*)-H_8-binap	96	47 (+)
2	(*S*)-binap	>99	21 (−)
3	(*R*)-tol-binap	>99	34 (+)
4	(*S*)-xyl-binap	>99	19 (−)
5	(*S*)-segphos	95	35 (−)
6	(*R*)-dtbm-segphos	>99	93 (+)

[a] $[Rh(cod)_2]BF_4$ (0.0050 mmol), ligand (0.0050 mmol), **1a** (0.10 mmol), **2a** (0.12 mmol), and CH_2Cl_2 (1.0 mL) were used. [b] Yield of isolated product.

biaryl bisphosphine ligands were screened and (*R*)-dtbm-segphos furnished (+)-**3aa** with the highest enantioselectivity (Table 1, entry 6).

The scope of this asymmetric cycloaddition was examined with respect to both cycloaddition partners at room temperature in the presence of the cationic rhodium(I)/(*R*)-dtbm-

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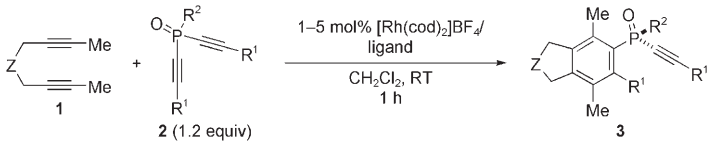
segphos complex (5 mol%) as shown in Table 2. In addition to ether-linked 1,6-diyne **1a**, methylene- and sulfonamide-linked 1,6-diynes **1b-d** (Table 2, entries 4–6) were found to be suitable substrates for this reaction. The use of (*S*)-dtbm-segphos as a ligand furnished the opposite enantiomer (e.g. (−)-**3aa**) with identical yields and *ee* values (Table 2, entry 2). Furthermore, the high catalytic activity of this rhodium catalyst enabled the reaction to be carried out with only 1 mol% of the catalyst (Table 2, entry 3). With respect to the dialkynylphosphine oxides, both electron-donating and electron-withdrawing groups, both of which can alter the electronic nature of the corresponding phosphorus compounds, could be introduced on the aryl groups at the alkyne terminus (**2b** and **2c**; Table 2, entries 7 and 8). However, the use of dialkynylphosphine oxide **2d** bearing a *n*-butyl group at the alkyne terminus significantly decreased both the yield and the enantioselectivity (Table 2, entry 9). Although the reactions of dialkynylphosphine oxides bearing a phenyl or *tert*-butyl group on the phosphorus center furnished the corresponding P-stereogenic alkynylphoshine oxides in high yields, moderate enantioselectivities were observed (Table 2, entries 10 and 11). The absolute configuration of P-stereogenic alkynylphosphine oxide (+)-**3da** was determined to be *S* by the anomalous dispersion method (Figure 1).[18]

Scheme 2 depicts a possible mechanism for the selective formation of P-stereogenic alkynylphosphine oxide (*S*)-**3da**. The reaction of diyne **1d** with rhodium and the subsequent coordination of dialkynylphosphine oxide **2a** to rhodium forms intermediate **A**; the arrangement results from the steric interaction between the alkynyl group of **2a** and the PAr_2 group of (*R*)-dtbm-segphos. Insertion of the alkynyl group and subsequent reductive elimination of rhodium gives (*S*)-**3da**.

Table 2: Rh-catalyzed desymmetrization of symmetrical dialkynylphosphine oxides **2a-f** with 1,6-diynes **1a-d**.[a]



Entry	1	Z	2	R^1	R^2	Ligand	Cat. [%]	3	Yield [%][b]	*ee* [%]
1	**1a**	O	**2a**	Ph	Me	(*R*)-dtbm-segphos	5	(+)-**3aa**	>99	93
2	**1a**	O	**2a**	Ph	Me	(*S*)-dtbm-segphos	5	(−)-**3aa**	>99	92
3[c]	**1a**	O	**2a**	Ph	Me	(*R*)-dtbm-segphos	1	(+)-**3aa**	91	93
4	**1b**	CH_2	**2a**	Ph	Me	(*R*)-dtbm-segphos	5	(+)-**3ba**	98	93
5	**1c**	NTs	**2a**	Ph	Me	(*R*)-dtbm-segphos	5	(+)-**3ca**	>99	85
6	**1d**	$NSO_2(4\text{-}BrC_6H_4)$	**2a**	Ph	Me	(*R*)-dtbm-segphos	5	(*S*)-(+)-**3da**	86	87
7	**1a**	O	**2b**	$4\text{-}MeOC_6H_4$	Me	(*R*)-dtbm-segphos	5	(+)-**3ab**	96	95
8	**1a**	O	**2c**	$4\text{-}F_3CC_6H_4$	Me	(*R*)-dtbm-segphos	5	(+)-**3ac**	83	91
9	**1a**	O	**2d**	*n*Bu	Me	(*R*)-dtbm-segphos	5	(−)-**3ad**	71	35
10	**1a**	O	**2e**	Ph	Ph	(*S*)-tol-binap	5	(−)-**3ae**	>99	50
11	**1a**	O	**2f**	Ph	*t*Bu	(*S*)-xyl-binap	5	(+)-**3af**	82	41

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), ligand (0.010 mmol), **1** (0.20 mmol), **2** (0.24 mmol), and CH_2Cl_2 (2.0 mL) were used. [b] Yield of isolated product. [c] The reaction was conducted by using $[Rh(cod)_2]BF_4$ (0.010 mmol), ligand (0.010 mmol), **1** (1.00 mmol), **2** (1.20 mmol), and CH_2Cl_2 (5.0 mL) at room temperature for 3 h and then at 40°C for 1 h (see Experimental Section).

The present asymmetric [2+2+2] cycloadditon was applied to the synthesis of C_2-symmetric P-stereogenic bis(alkynylphosphine oxide) (Scheme 3). The reaction of tetrayne **4** with diyne **1a** (2.4 equiv) at 80°C in the presence of a cationic rhodium(I)/(*R*)-xyl-binap complex (10 mol%) selectively furnished the desired double annulation product as a mixture of diastereomers in quantitative yield with moderate enantioselectivity. Fortunately, pure *dl*-isomer (−)-**5** was readily obtained with a high *ee* value by recrystallization.

In conclusion, we have developed an enantioselective synthesis of P-stereogenic alkynylphosphine oxides[19] by a [2+2+2] cycloaddition of symmetrical dialkynylphosphine oxides with 1,6-diynes catalyzed by a cationic rhodium(I) complexed with a modified binap ligand. Furthermore, this method allows generation of a C_2-symmetric P-stereogenic bis(alkynylphosphine oxide).[19] Utilization of the new P-stereogenic alkynylphosphorus compounds for asymmetric reactions is underway in our laboratory.

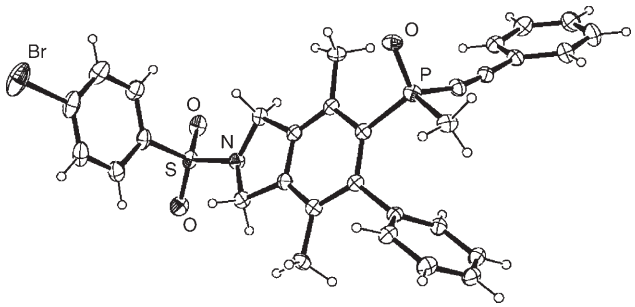
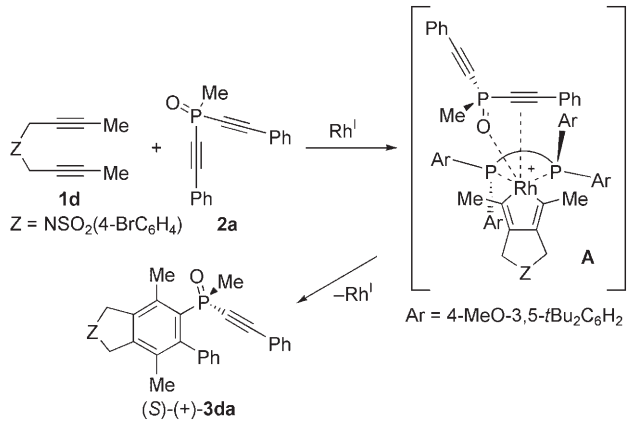


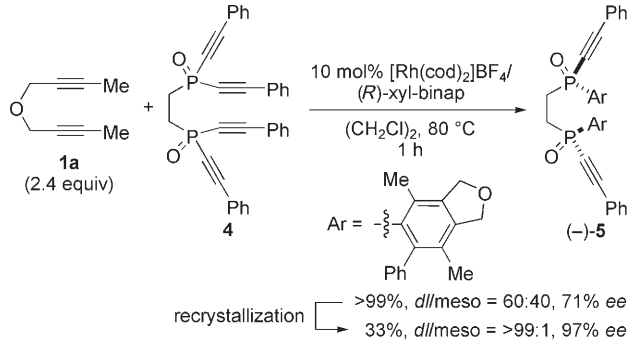
Figure 1. ORTEP drawing of (*S*)-(+)-**3da** (product of Table 2, entry 6) drawn at the 30% probability level.

Experimental Section

Representative procedure (Table 2, entry 3): (*R*)-dtbm-segphos (11.8 mg, 0.010 mmol, 1 mol%) and $[Rh(cod)_2]BF_4$ (4.1 mg, 0.010 mmol, 1 mol%) were dissolved in CH_2Cl_2 (1.0 mL) and the solution was stirred at room temperature for 5 min under Ar. H_2 (1 atm) was introduced to the resulting solution that was contained in a Schlenk tube, stirred at room temperature for 1 h, and then concentrated to dryness and re-dissolved in CH_2Cl_2 (0.4 mL). A CH_2Cl_2 (1.6 mL) solution of **2a** (317.1 mg, 1.20 mmol) was added to the reaction mixture and then was a CH_2Cl_2 (3.0 mL) solution of diyne **1a** (122.1 mg, 1.00 mmol) was added over a 15 min period at room temperature. After stirring at room temperature for 3 h and then at 40°C for 1 h, the resulting solution was concentrated and



Scheme 2. Possible mechanism for the selective formation of (*S*)-(+)-**3da**.



Scheme 3. Rh-catalyzed enantioselective synthesis of C_2-symmetric P-stereogenic bis(alkynylphosphine oxide) (−)-**5**.

purified by silica gel column chromatography (hexane/EtOAc/Et_3N = 3:1:1), to furnish (+)-**3aa** (352.7 mg, 0.91 mmol, 91 % yield, 93 % *ee*) as a pale yellow oil. $[\alpha]^{25}_D$ +152.4 deg cm^3 g^{-1} dm^{-1} (c = 3.96 g cm^{-3} in $CHCl_3$, 93 % *ee*); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.51–7.11 (m, 10 H), 5.20 (s, 2 H), 5.15 (s, 2 H), 2.79 (s, 3 H), 1.82 (s, 3 H), 1.17 ppm (d, J = 15.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 143.4, 143.3, 141.68, 141.65, 139.62, 139.56, 139.3, 139.1, 134.4, 134.3, 132.02, 132.00, 131.5, 130.7, 130.1, 130.0, 129.9, 128.5, 128.4, 128.3, 128.2, 127.9, 127.7, 120.43, 120.38, 102.1, 101.7, 87.7, 85.6, 74.28, 74.26, 74.2, 22.6, 21.4, 19.5, 19.4, 16.94, 16.93 ppm; ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 12.4 ppm; IR (neat): $\tilde{\nu}$ = 2173, 1171, 897, 757 cm^{-1}; HRMS (FAB): calcd for $C_{25}H_{24}O_2P$: 387.1514, found: 387.1516 $[M+H]^+$; CHIRALPAK AD-H, hexane/2-PrOH = 90:10, 1.0 mL min^{-1}, retention times: 25.7 min (major isomer) and 33.9 min (minor isomer).

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[18] CCDC 671150 [(*S*)-(+)-**3da**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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