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Enantioselective Synthesis of Axially Chiral Hydroxy Carboxylic Acid Derivatives by Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition

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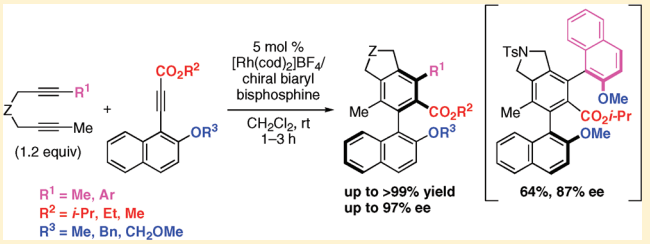
Supporting Information

ABSTRACT: Axially chiral hydroxy carboxylic acid derivatives were successfully synthesized with high yields and ee values by the cationic rhodium(I)/axially chiral biaryl bisphosphine complex-catalyzed enantioselective [2 + 2 + 2] cycloaddition. Axially chiral hydroxy and dihydroxy carboxylic acid derivatives, bearing the aryl group at the *ortho*-position of the alkoxycarbonyl group, were also synthesized with high regio- and enantioselectivity.



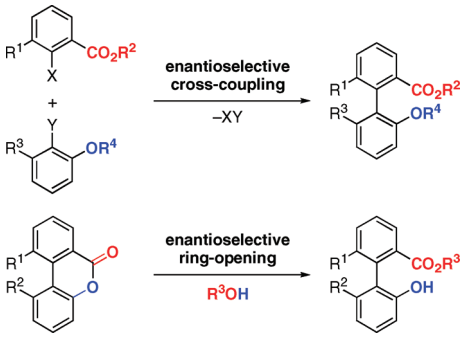
Functionalized axially chiral biaryls are important compounds as various chiral ligands, catalysts, and optical resolution agents.[1] For example, axially chiral hydroxy carboxylic acid derivatives, such as 2′-methoxy-1,1′-binaphthyl-2-carboxylic acid, were used as chiral derivatizing agents for determination of enantiomeric purities and absolute configurations of optically active alcohols and amines.[2] These are also useful starting materials for the synthesis of axially chiral biarylamide-[3] and biarylamine-derived ligands[4] and axially chiral ammonium betaine organocatalysts.[5] Therefore, their asymmetric synthesis has been well investigated to date, and several successful examples have been reported.[6−9] As a cross-coupling approach, the diastereoselective nucleophilic aromatic substitution on chiral 1-alkoxy-2-naphtholates with aryl Grignard reagents[2a,b,6] and the enantioselective Suzuki−Miyaura cross-coupling[7] were reported (Scheme 1). As a conceptually different approach, a number of enantioselective ring-opening reactions of biaryl lactones, possessing configurationally unstable biaryl axes, were reported (Scheme 1).[8]

On the other hand, our research group reported the asymmetric synthesis of functionalized biaryl compounds by the cationic rhodium(I)/axially chiral biaryl bisphosphine complex-catalyzed enantioselective [2 + 2 + 2] cycloaddition.[10−13] We report herein the enantioselective synthesis of axially chiral hydroxy carboxylic acid derivatives,[14] which consist of one naphthol and one benzoic acid moiety, by the rhodium-catalyzed [2 + 2 + 2] cycloaddition (Scheme 2). The enantioselective benzannulation by the rhodium-catalyzed [2 + 2 + 2] cycloaddition is highly attractive because of not only high catalytic activity and enantioselectivity but also facile introduction of various substituents at the *ortho*-position of the alkoxycarbonyl group (R^1, Scheme 2) upon benzannulation.

We first investigated the reaction of 2-methoxynaphthalene-derived alkynylester **2a** with ether-linked 1,6-diyne **1a** (1.2 equiv) in the presence of the cationic rhodium(I)/(*S*)-BINAP complex (5 mol %). Pleasingly, the reaction proceeded at room temperature for only 1 h to give the desired [2 + 2 + 2] cycloaddition product **3aa** with high yield and enantioselectivity (Table 1, entry 1). It was found that the steric bulk of the alkoxycarbonyl group exhibits a modest impact on yield and enantioselectivity (entries 1−3). The highest yield and enantioselectivity were obtained by using sterically demanding *i*-propyl ester **2c** (entry 3).

Effect of axially chiral biaryl bisphosphine ligands (Figure 1) on yield and enantioselectivity was also examined as shown in Table 2. Among the bis(diphenylphosphine) ligands examined (entries 1−3), the use of (*S*)-BINAP furnished **3aa** with the highest

Scheme 1



Scheme 2

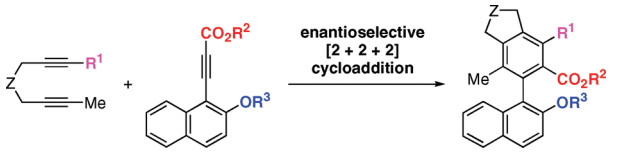


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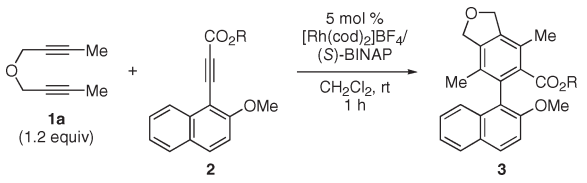
Table 1. Effect of Alkoxyl Groups of Monoynes 2a−c on Rh-Catalyzed Enantioselective [2 + 2 + 2] Cycloaddition with 1,6-Diyne 1a



entry	2	R	3	yield[a] (%)	ee (%)
1	**2a**	Me	(+)-**3aa**	88	91
2	**2b**	Et	(+)-**3ab**	99	94
3	**2c**	*i*-Pr	(+)-**3ac**	>99	96

[a] Isolated yield.

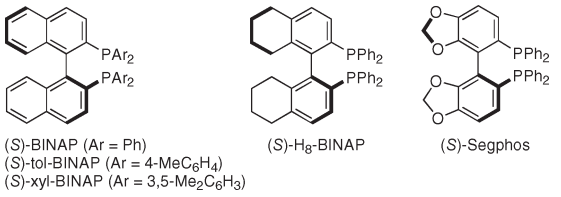
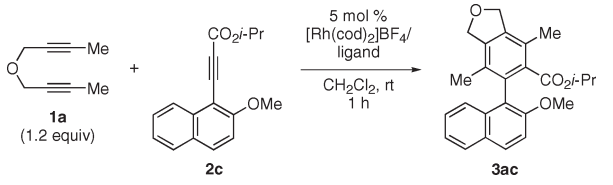


Figure 1. Structures of axially chiral biaryl bisphosphine ligands.

Table 2. Effect of Ligands on Rh-Catalyzed Enantioselective [2 + 2 + 2] Cycloaddition of 1,6-Diyne 1a with Monoyne 2c



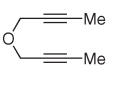
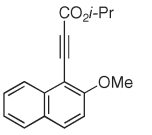
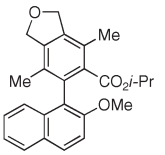
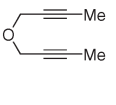
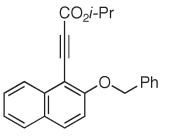
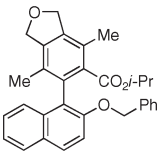
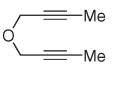
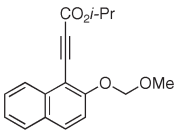
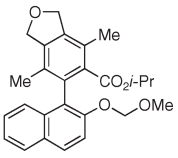
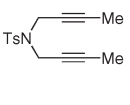
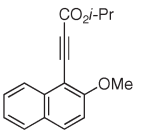
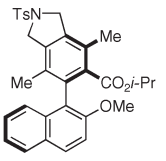
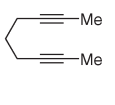
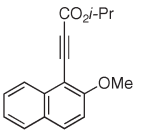
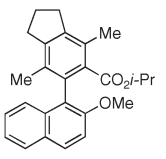
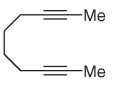
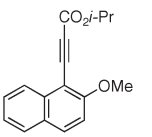
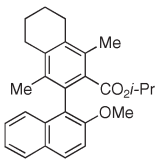
entry	ligand	yield[a] (%)	ee (%)
1	(*S*)-BINAP	>99	96 (+)
2	(*S*)-H_8−BINAP	97	94 (+)
3	(*S*)-Segphos	97	88 (+)
4	(*S*)-tol-BINAP	99	96 (+)
5	(*S*)-xyl-BINAP	99	91 (+)
6	(*R*)-BINAP	97	95 (−)

[a] Isolated yield.

enantioselectivity (entry 1). The effect of the steric bulk of the aryl group on the phosphorus of BINAP was then examined. The study revealed that the use of (*S*)-BINAP and (*S*)-tol-BINAP provided the same yields and enantioselectivities (entries 1 and 4), while that of (*S*)-xyl-BINAP decreased the enantioselectivity (entry 5). The use of (*R*)-BINAP instead of (*S*)-BINAP furnished the opposite enantiomer with almost identical yield and ee value (entry 6).

Thus, we tested the generality of the reaction with respect to both cycloaddition partners as shown in Table 3. With respect to the substituents at the 2-position of the 1-alkynylnaphthalene, not only methoxy (**2c**, entry 1) but also benzyloxy and methoxymethoxy derivatives **2d** and **2e** (entries 2 and 3) were suitable substrates for this process. With respect to the diynes, not only ether-linked 1,6-diyne **1a** but also tosylamide-linked 1,6-diyne **1b** (entry 4) and methylene-linked 1,6-diyne **1c** (entry 5) were suitable substrates for this process.

Table 3. Rh-Catalyzed Enantioselective [2 + 2 + 2] Cycloaddition of Symmetrical 1,6- and 1,7-Diynes 1a−d with Monoynes 2c−e[a]

entry	1 (Z)	2 (R)	3 / % yield[b] (% ee)
1	 **1a**	 **2c**	 (+)-**3ac** / >99 (96)
2	 **1a**	 **2d**	 (+)-**3ad** / 91 (89)
3	 **1a**	 **2e**	 (+)-**3ae** / 95 (91)
4	 **1b**	 **2c**	 (*R*)-(+)-**3bc** / >99 (90)
5	 **1c**	 **2c**	 (+)-**3cc** / 93 (97)
6	 **1d**	 **2c**	 (+)-**3dc** / 71 (93)

[a] Reactions were conducted using $[Rh(cod)_2]BF_4$ (5 mol %), (*S*)-BINAP (5 mol %), **1a−d** (1.2 equiv), and **2c−e** (1 equiv) in CH_2Cl_2 at room temperature for 1 h. [b] Isolated yield.

Furthermore, 1,7-diyne **1d** (entry 6) was able to react with **2c** to give the corresponding biaryl **3dc** in good yield with high ee value. The absolute configuration of the biaryl (+)-**3bc** was unambiguously determined to be *R* by an X-ray crystallographic analysis.[15]

The following two experiments clearly indicated that the 2-methoxynaphthalene unit is necessary to achieve high enantioselectivity. The reaction of 2-methoxybenzene-derived alkynylester **2f** with **1a** in the presence of the cationic rhodium(I)/(*S*)-BINAP complex at room temperature furnished the corresponding biaryl **3af** in excellent yield, while the ee value was extremely low (Scheme 3). The reaction of 2-methylnaphthalene-derived alkynyl ester **2g** with **1a** was also examined under the same reaction conditions, which furnished the corresponding biaryl **3ag** in good yield with low ee

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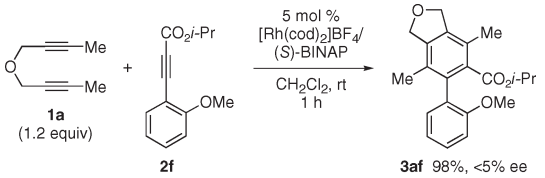
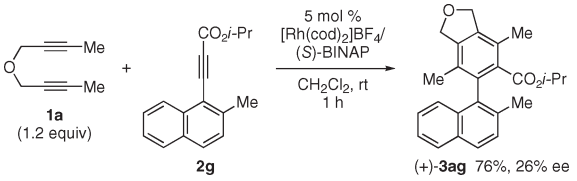
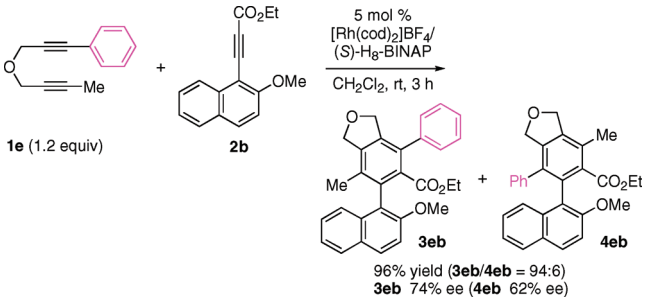
Scheme 3



Scheme 4



Scheme 5

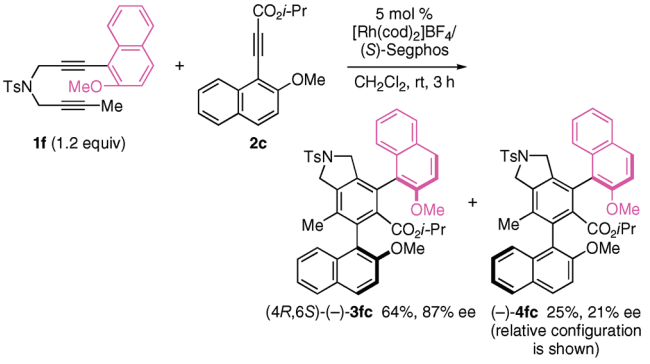


value (Scheme 4). Therefore, both the naphthalene moiety and the methoxy group are essential for high enantioselection.

As aryl substitution at the *ortho*-position of the alkoxycarbonyl group is important for the synthesis of axially chiral organocatalysts,[5] the reaction of unsymmetrical 1,6-diyne **1e**, possessing phenyl and methyl at each alkyne terminus, and **2b** was examined (Scheme 5). Pleasingly, the desired biaryl **3eb**, bearing the phenyl group at the *ortho*-position of the ethoxycarbonyl group, was obtained in high yield with good ee value along with a small amount of minor regioisomer **4eb** by using the cationic rhodium(I)/(*S*)-H_8-BINAP catalyst.[16]

Finally, the enantio- and diastereoselective synthesis of a 1,3-teraryl compound, possessing the protected dihydroxy carboxylic acid structure, was examined (Scheme 6). The reaction of 2-methoxynaphthalene-derived 1,6-diyne **1f** and **2c** proceeded with perfect regioselectivity by using the cationic rhodium(I)/(*S*)-Segphos catalyst to give the desired 1,3-teraryl compound **3fc** as a major diastereomer with good yield and ee value along with minor diastereomer **4fc**. The relative and absolute configurations of the 1,3-teraryl (−)-**3fc** was unambiguously determined to be 4*R*,6*S* by an X-ray crystallographic analysis. Interestingly, the absolute configuration (*S*) of the axial chirality derived from monoyne **2c** is opposite to that of (+)-**3bc** (*R*). Therefore, the axial chirality derived from diyne **1f** would be determined enantioselectively by the ligand and that derived from monoyne **2c** would be subsequently determined diastereoselectively.[15]

Scheme 6



In conclusion, axially chiral hydroxy carboxylic acid derivatives were successfully synthesized at room temperature with high yields and ee values by the cationic rhodium(I)/axially chiral biaryl bisphosphine complex-catalyzed enantioselective [2 + 2 + 2] cycloaddition. Axially chiral hydroxy and dihydroxycarboxylic acid derivatives, bearing the aryl group at the *ortho*-position of the alkoxycarbonyl group, were also synthesized with high regio- and enantioselectivity. Future work will focus on application of new axially chiral hydroxy and dihydroxy carboxylic acid derivatives in organic synthesis.

EXPERIMENTAL SECTION

Typical Procedure for the Rhodium-Catalyzed Enantioselective [2 + 2 + 2] Cycloaddition (Table 3, Entry 1). (*S*)-BINAP (6.2 mg, 0.010 mmol) and $[Rh(cod)_2]BF_4$ (4.1 mg, 0.010 mmol) were dissolved in CH_2Cl_2 (1.0 mL), and the mixture was stirred at room temperature for 5 min. H_2 (1 atm) was introduced to the resulting solution in a Schlenk tube. After being stirred at room temperature for 1 h, the resulting solution was concentrated and dissolved in CH_2Cl_2 (0.4 mL). To this solution was added a CH_2Cl_2 (0.4 mL) solution of **2c** (53.7 mg, 0.200 mmol), and then a CH_2Cl_2 (1.2 mL) solution of **1a** (29.3 mg, 0.240 mmol) was added dropwise over 20 min at room temperature. After being stirred at room temperature for 1 h, the resulting solution was concentrated and purified by preparative TLC (toluene/EtOAc = 10:1), which furnished (+)-**3ac** (77.9 mg, 0.199 mmol, >99% yield, 96% ee) as a yellow solid: mp 35.4−36.6 °C; $[\alpha]^{25}_D$ +50.8 (*c* 3.76, $CHCl_3$, 96% ee); IR (KBr) 2978, 1720, 1594, 1466, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.87 (d, *J* = 9.0 Hz, 1H), 7.80−7.73 (m, 1H), 7.36−7.27 (m, 3H), 7.25−7.17 (m, 1H), 5.26−5.16 (m, 4H), 4.59 (sept, *J* = 6.3 Hz, 1H), 3.86 (s, 3H), 2.25 (s, 3H), 1.78 (s, 3H), 0.69 (d, *J* = 6.3 Hz, 3H), 0.42 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.4, 154.2, 139.0, 137.7, 135.2, 133.5, 133.3, 129.4, 128.7, 128.5, 127.5, 126.3, 125.5, 125.2, 123.4, 121.3, 113,1, 74.1, 74.0, 67.6, 56.5, 21.0, 20.5, 16.3, 15.9; HRMS (ESI) calcd for $C_{25}H_{26}O_4Na$ $[M + Na]^+$ 413.1723, found 413.1731; CHIRALPAK IC, hexane/THF = 95:5, 0.5 mL/min, retention times 22.2 min (minor isomer) and 24.9 min (major isomer).

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, compound characterization data, and X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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