Biaryl Compounds

Enantioselective Synthesis of Axially Chiral Phthalides through Cationic [Rh^{I}(H_8-binap)]-Catalyzed Cross Alkyne Cyclotrimerization**

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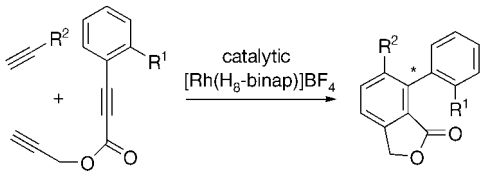
Axially chiral biaryl compounds are widely found as key structures of effective chiral ligands and biologically active compounds. Therefore, several catalytic enantioselective syntheses of these compounds have been developed to date. These methods are based on three types of asymmetric cross-coupling approaches: 1) cross-coupling of aryl compounds (such as the Kumada coupling,[1] Suzuki coupling,[2] and oxidative coupling[3]), 2) cross-coupling of biaryl ditriflates,[4] and 3) cross-coupling of dinaphthothiophene.[5] In these reactions, the axial chirality is constructed during the formation of the biaryl link, the selective substitution of one of two triflates, and the selective cleavage of one of two carbon–sulfur bonds, respectively.[6,7]

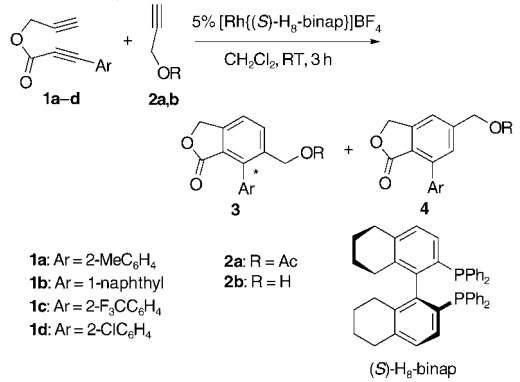
Cyclotrimerization of alkynes is an attractive method for the synthesis of substituted benzenes, and various transition-metal complexes catalyze this reaction.[8] We recently reported the chemo- and regioselective intermolecular cross cyclotrimerization of terminal alkynes and an electron-deficient alkyne (diethyl acetylene dicarboxylate) catalyzed by the cationic [Rh^{I}(H_8-binap)][9] complex.[10] We anticipated that cross cyclotrimerization of terminal alkynes and electron-deficient 1,6-diynes (bearing a *ortho*-substituted phenyl group and a hydrogen atom at each terminal position) would install the axial chirality during the formation of the benzene rings (Scheme 1).[11–14] Very recently, Gutnov, Heller, and co-workers reported the synthesis of axially chiral 2-aryl pyridines through the Co^{I}-catalyzed asymmetric [2+2+2] cycloaddition of alkynes and nitriles,[15] and Shibata et al. reported the synthesis of axially chiral teraryl compounds through a neutral [Ir^{I}(Me-duphos)] complex catalyzed asymmetric [2+2+2] cycloaddition of symmetrical α,ω-diynes and symmetrical monoynes.[16] Herein we describe a highly enantioselective synthesis of axially chiral phthalides by the cationic [Rh^{I}(H_8-binap)] complex catalyzed cross alkyne cyclotrimerization of unsymmetrical α,ω-diynes and unsymmetrical or symmetrical monoynes.[17]



Scheme 1. Cationic [Rh^{I}(H_8-binap)]-catalyzed cross alkyne cyclotrimerization to give axially chiral phthalides.

The reaction of 2-methylphenyl-substituted 1,6-diyne **1a** with various terminal monoynes was investigated in the presence of the cationic complex [Rh^{I}{(*S*)-H_8-binap}]. We were pleased to find that the use of propargyl acetate (**2a**; 5 equiv) furnished axially chiral phthalide (+)-**3aa** in high yield with high enantioselectivity (Table 1, entry 1). Not only

Table 1: Enantioselective cross alkyne cyclotrimerization of 1,6-diynes **1** and terminal monoynes **2**.



Entry	1	2	Phthalide	Yield [%][a]	3/4	*ee* (3) [%]
1	**1a**	**2a**	(+)-**3aa**/**4aa**	79	90:10	87
2	**1b**	**2a**	(−)-**3ba**/**4ba**	91	88:12	82
3	**1c**	**2a**	(−)-**3ca**/**4ca**	86	66:34	81
4	**1d**	**2a**	(−)-**3da**/**4da**	91	87:13	73
5	**1a**	**2b**	(+)-**3db**/**4db**	90	70:30	78

[a] Yields of isolated products.

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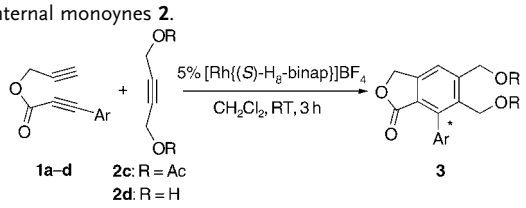
2-methylphenyl-, but also 1-naphthyl- (**1b**, Table 1, entry 2), 2-trifluoromethylphenyl- (**1c**, Table 1, entry 3), and 2-chlorophenyl-substituted 1,6-diynes (**1d**, Table 1, entry 4) were suitable substrates in this process. Importantly, the generation of sterically demanding regioisomers **3** was predominant. In the case of **1d**, the use of propargyl alcohol (**2b**) improved the enantioselectivity (Table 1, entry 5).

Interestingly, the use of symmetrical internal monoyne, 1,4-diacetoxy-2-butyne (**2c**; 5 equiv), enhanced the enantioselectivity to yield axially chiral phthalides **3ac**–**dc** in good yield with excellent enantioselectivity (Table 2, entries 1–4).

Table 2: Enantioselective cross alkyne cyclotrimerization of 1,6-diynes **1** and internal monoynes **2**.



1a–d **2c**: R = Ac, **2d**: R = H **3**

Entry	1	2	Phthalide	Yield [%][a]	*ee* [%]
1	**1a**	**2c**	(+)-**3ac**	67	>99
2	**1b**	**2c**	(+)-**3bc**	57	94
3	**1c**	**2c**	(+)-**3cc**	73	>99
4	**1d**	**2c**	(+)-**3dc**	45	86
5[b]	**1a**	**2d**	(+)-**3dd**	63	>99

[a] Yields of isolated products. [b] Solvent: THF.

In the case of **1d**, the use of 2-butyne-1,4-diol (**2d**) improved the yield and enantioselectivity (Table 2, entry 5). The absolute configuration of the diol (+)-**3dd** was determined to be *R* by an anomalous dispersion method, and that of the diacetate (+)-**3dc** was also determined to be *R* (Figure 1).[18]

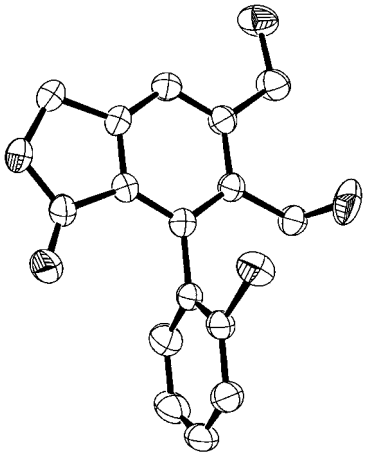
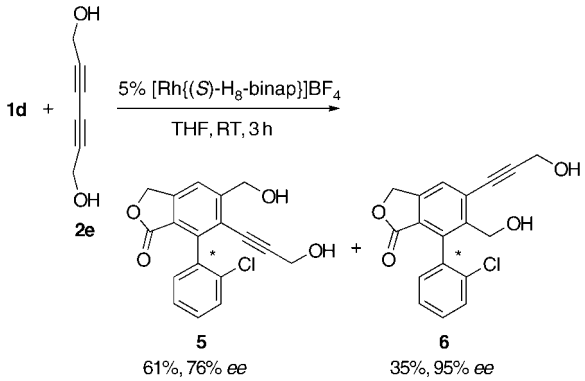


Figure 1. ORTEP Diagram of (*R*)-(+)-**3dd** drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.

The present enantioselective cross alkyne cyclotrimerization was applied to the symmetrical internal diyne **2e**, and the chiral phthalides **5** and **6** were obtained in excellent yield with high enantioselectivity (Scheme 2).



Scheme 2. Cross alkyne cyclotrimerization of **1d** and symmetrical internal diyne **2e**.

In conclusion, we have discovered an enantioselective cross alkyne cyclotrimerization of unsymmetrical 1,6-diynes and both terminal and internal alkynes. This method provides easy access to axially chiral phthalides that bear one or two oxymethylene functionalities. Work toward developing a wide variety of asymmetric reactions in the presence of cationic complexes of Rh^{I} and modified binap is underway in our laboratory.

Experimental Section

Full procedures and characterization data are given in the Supporting Information.**3ac**: Under an Ar atmosphere, (*S*)-H_8-binap (7.9 mg, 0.0125 mmol) and $[Rh(cod)_2]BF_4$ (5.1 mg, 0.0125 mmol) were dissolved in CH_2Cl_2 (1.0 mL), and the mixture was stirred for 5 min. H_2 was introduced to the resulting solution in a Schlenk tube. The resulting mixture was stirred for 30 min at room temperature and then concentrated to dryness. The residue was taken up in CH_2Cl_2 (1.0 mL), and to this solution was added a solution of **1a** (49.8 mg, 0.250 mmol) and **2c** (212.7 mg, 1.25 mmol) in CH_2Cl_2 (1.0 mL) at room temperature; the vial was rinsed with CH_2Cl_2 (0.5 mL). The mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated and purified by preparative TLC to furnish (+)-**3ac** (61.7 mg, 0.167 mmol, 67%, >99% *ee*) as a yellow solid. M.p. 95.0–97.5 °C; $[\alpha]_D^{25} = +17.3°$ ($c = 0.274$, $CHCl_3$); IR (neat): $\tilde{\nu} =$ 1740, 1220, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.60$ (s, 1H), 7.22–7.36 (m, 3H), 7.01 (dd, $J = 7.6$ and 1.2 Hz, 1H), 5.33 (s, 2H), 5.29 (d, $J = 3.2$ Hz, 2H), 4.99 (d, $J = 12.8$ Hz, 1H), 4.88 (d, $J = 12.8$ Hz, 1H), 2.17 (s, 3H), 1.98 (s, 3H), 1.97 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 170.3$, 170.0, 168.6, 147.5, 143.2, 142.6, 135.8, 133.7, 133.2, 129.7, 128.6, 128.5, 125.5, 123.4, 121.5, 68.2, 63.4, 59.8, 20.9, 20.6, 20.0 ppm; HRMS (EI): calcd for $C_{21}H_{20}O_6$ $[M]^+$: 368.1260; found: 368.1226; CHIRALPAK AS, hexane/*i*PrOH 80:20, 0.8 mL min^{-1}, retention times: 28.6 min (minor isomer) and 30.3 min (major isomer).

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[18] CCDC-246690 (**3dd**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

