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Enantioselective Synthesis of Tetra-*ortho*-Substituted Axially Chiral Biaryls through Rhodium-Catalyzed Double [2 + 2 + 2] Cycloaddition

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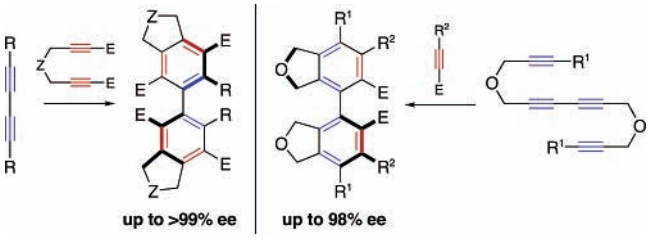
ABSTRACT



We have established an enantioselective synthesis of both C_2 symmetric and unsymmetric tetra-*ortho*-substituted axially chiral biaryls through rhodium-catalyzed double [2 + 2 + 2] cycloaddition (up to >99% ee). This method serves as an attractive new route to enantioenriched tetra-*ortho*-substituted axially chiral biaryls in view of the one-step access to substrate diynes and tetraynes starting from readily available alkynes.

Tetra-*ortho*-substituted biaryls, having highly stable axial chirality, are valuable structures for chiral ligands used in a variety of asymmetric reactions,[1] and various enantioselective methods for their synthesis have been reported to date.[2] In general, these are based on transition-metal-catalyzed cross- or homo-coupling of two aryl units where the axial chirality is constructed at the formation of the aryl−aryl bond.[3−9] The enantioselective coupling of sterically encumbered 2,6-disubstituted arenes, which furnishes tetra-*ortho*-substituted

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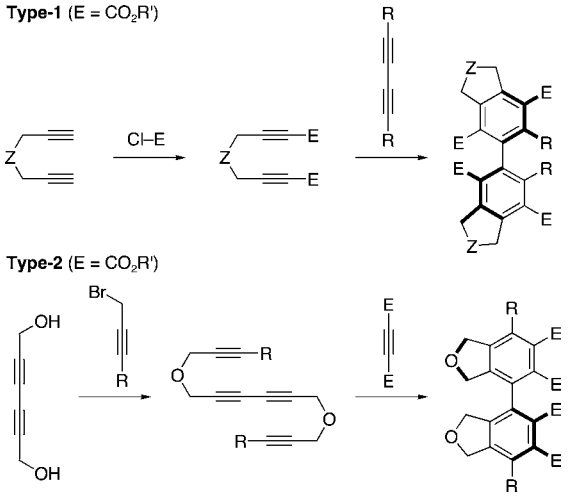
biaryls, has been realized in several examples, e.g., nickel- or palladium-catalyzed cross-coupling of *unfunctionalized* 2,6-disubstituted arenes,[3,4b] oxidative homo-coupling of 2-naphthol derivatives,[5] and Grignard cross-coupling of dibenzothiophenes.[7] However, the efficient catalytic method, which can be applicable to the enantioselective synthesis of *functionalized* axially chiral tetra-*ortho*-substituted biaryls, is an important challenge.

Recently, a new approach to the synthesis of axially chiral tri-*ortho*-substituted biaryls has been developed, which is based on an enantioselective [2 + 2 + 2] cycloaddition[10,11] between internal alkynes bearing an *ortho*-substituted phenyl group and nitriles,[12] isocyanates,[13] or alkynes.[14−18] We anticipated that an enantioselective two-step synthesis of C_2 symmetric tetra-*ortho*-substituted axially chiral biaryls could be realized through double [2 + 2 + 2] cycloaddition of electron-deficient 1,6-diynes, prepared in one step from readily available terminal 1,6-diynes, with 1,3-diynes (Scheme 1, Type-1) or ether-linked tetraynes, prepared in one step

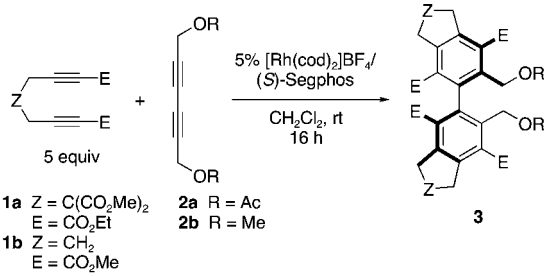
Scheme 1. Enantioselective Two-Step Synthesis of C_2 Symmetric Tetra-*ortho*-Substituted Axially Chiral Biaryls



from readily available 2,4-hexadiyne-1,6-diol, with electron-deficient monoynes (Scheme 1, Type-2).[19] In this Communication, we describe an enantioselective synthesis of functionalized tetra-*ortho*-substituted axially chiral biaryls through rhodium-catalyzed double [2 + 2 + 2] cycloaddition.

We first investigated the reaction of electron-deficient malonate-derived 1,6-diyne **1a** and 1,3-diyne **2a** in the presence of various Rh(I)$^+$/modified-BINAP complexes (Type-1).[20] We were pleased to find that the use of 5% Rh(I)$^+$/(*S*)-Segphos [(4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine)][21] complex furnished the corresponding C_2 symmetric tetra-*ortho*-substituted biaryl (−)-**3aa** in 59% yield with >99% ee (Table 1, entry 1). Not only diacetoxy-substituted 2,4-hexadiyne **2a** but also dimethoxy-substituted

Table 1. Enantioselective Synthesis of C_2 Symmetric Tetra-*ortho*-Substituted Axially Chiral Biaryls **3**



entry	1	2	3	yield (%)[a]	ee (%)
1	**1a**	**2a**	(−)-**3aa**	59	>99
2	**1a**	**2b**	(−)-**3ab**	48	98
3	**1b**	**2a**	(*R*)-(+)-**3ba**	30 (56[b])	>99

[a] Isolated yield. [b] Isolated yield of mono-annulation product **4** (Scheme 2).

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2,4-hexadiyne **2b** are suitable substrates in this process, and biaryl (−)-**3ab** was obtained in 48% yield with 98% ee (entry 2). In these reactions, mono-annulation products were generated as byproducts. The use of 1,6-diyne **1b**, having no quaternary center in the tether, furnished mono-annulation product **4** in 56% yield as a major product, although biaryl (+)-**3ba** was obtained in 30% yield with >99% ee (entry 3). The X-ray crystallographic analysis revealed the *R* configuration for the biaryl (+)-**3ba** (Figure 1).

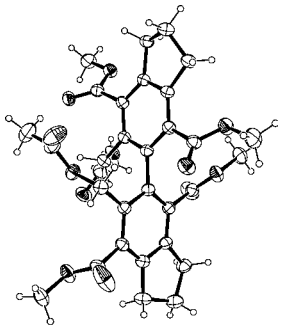
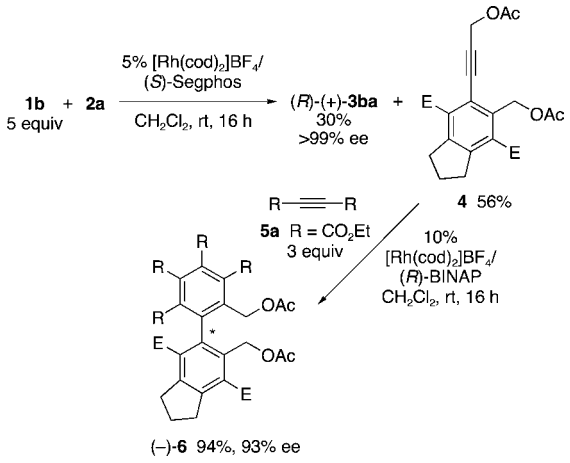


Figure 1. ORTEP diagram of (*R*)-(+)-**3ba**.

The isolated mono-annulation product **4** could be used for the enantioselective complete intermolecular [2 + 2 + 2] cycloaddition with diethyl acetylenedicarboxylate (**5a**) using 10% Rh(I)$^+$/(*R*)-BINAP complex as catalyst, and unsymmetrical tetra-*ortho*-substituted biaryl (−)-**6** was obtained in 94% yield with 93% ee (Scheme 2).[15b]

Scheme 2. Enantioselective Synthesis of Unsymmetrical Tetra-*ortho*-Substituted Axially Chiral Biaryl **6**



Next, the reaction of terminal tetrayne **7a** with electron-deficient monoyne **5b** was investigated (Type-2). After screening various Rh(I)$^+$/modified-BINAP complexes, we found that the use of 5% Rh(I)$^+$/(*S*)-Segphos complex furnished the corresponding C_2 symmetric axially chiral biaryl (+)-**8ab** with excellent ee (98% ee), although the yield was low (Table 2, entry 1). The use of methyl-substituted internal tetrayne **7b** or terminal monoyne **5c** instead of **7a** or **5c** increased the yield of the corresponding biaryls to 52% or 44%, respectively, but decreased the ee to 69% or 70% (entries 2 and 3). The X-ray crystallographic analysis revealed *S* configuration for the biaryl (+)-**8bb** (Figure 2). Importantly, this double [2 + 2 + 2] cycloaddition could be applied to the axially chiral bipyridine synthesis using ethyl cyanoformate **5d**, which furnished bipyridine (+)-**8bd** in

Table 2. Enantioselective Synthesis of C_2 Symmetric Tetra-*ortho*-Substituted Axially Chiral Biaryls **8**
[5% [Rh(cod)$_2$]BF$_4$/(*S*)-Segphos, CH_2Cl_2, rt, 16 h]

entry	7	5, equiv	8, yield (%),[a] ee (%)
1	**7a** R = H	**5b**, 10	(+)-**8ab**, 24, 98
2	**7b** R = Me	**5b**, 2.5	(*S*)-(+)-**8bb**, 52, 69
3[b]	**7a**	**5c**, 5	**8ac**, 44, 70
4	**7b**	**5d**, 10	(+)-**8bd**, 38, 98
5	**7c**	**5e**, 2.1	(−)-**8ce**, 89, 52

[a] Isolated yield. [b] Isolated as a mixture of **8ac** and another regioisomer. Yield of **8ac** was determined by ^{1}H NMR. The corresponding diol of **8ac** was isolated in pure form in 77% isolated yield from **8ac** by treatment with LiAlH$_4$.

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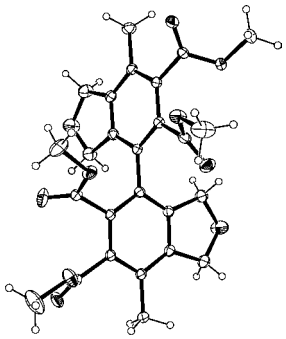


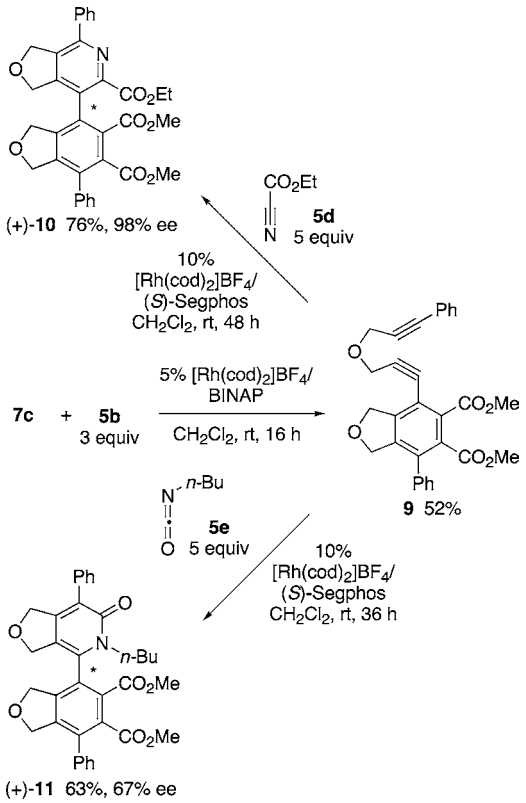
Figure 2. ORTEP diagram of (*S*)-(+)-**8bb**.

38% yield with 98% ee, although achiral regioisomers were generated in >50% yield (entry 4). Furthermore, the reaction of phenyl-substituted tetrayne **7c** with isocyanate **5e** furnished bipyridone (−)-**8ce** in 89% yield with 52% ee (entry 5).

Interestingly, the reaction of phenyl-substituted tetrayne **7c** with **5b** in the presence of 5% $Rh(I)^+$/(*S*)-Segphos complex furnished mono-annulation product **9** in 35% yield, and no corresponding biaryl was generated. The use of $Rh(I)^+$/BINAP complex improved the yield of **9** to 52%. The isolated mono-annulation product **9** could be used for the enantioselective [2 + 2 + 2] cycloaddition with nitrile **5d** and isocyanate **5e** using $Rh(I)^+$/(*S*)-Segphos complex as catalyst, which furnished axially chiral aryl pyridine (+)-**10** in 76% yield with 98% ee and axially chiral aryl pyridone (+)-**11** in 63% yield with 67% ee, respectively (Scheme 3).

In conclusion, we have established an enantioselective synthesis of both C_2 symmetric and unsymmetric tetra-*ortho*-substituted axially chiral biaryls through rhodium-catalyzed double [2 + 2 + 2] cycloaddition. This method serves as an attractive new route to enantioenriched tetra-*ortho*-substituted axially chiral biaryls in view of the one-step access to substrate diynes and tetraynes starting from readily available

Scheme 3. Enantioselective Synthesis of Unsymmetrical Tetra-*ortho*-Substituted Axially Chiral Biaryls **10** and **11**



alkynes. Expanding the scope and exploration of the mechanism of enantioselection are currently under investigation.

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

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