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Enantioselective Synthesis of Axially Chiral Biaryls through Rhodium-Catalyzed Complete Intermolecular Cross-Cyclotrimerization of Internal Alkynes

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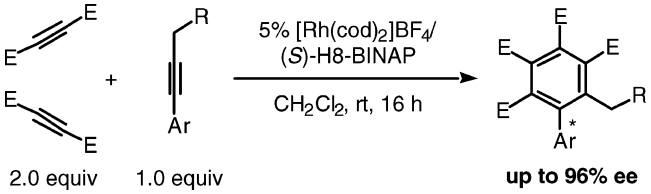
ABSTRACT



We have developed a cationic rhodium(I)/H8-BINAP complex-catalyzed complete intermolecular cross-cyclotrimerization of internal alkynes with dialkyl acetylenedicarboxylates. This reaction was successfully applied to enantioselective synthesis of axially chiral biaryls utilizing internal alkynes bearing ortho-substituted phenyl and acetoxymethyl in each terminal position. The axial chirality is constructed at the formation of benzene rings with high enantioselectivity (up to 96% ee).

Axially chiral biaryls are valuable structures for chiral ligands and biologically active compounds,[1,2] and various enantioselective methods for their synthesis have been reported to date.[3−5] These are mainly based on transition-metal-catalyzed enantioselective cross-coupling approaches.[3] Recently, a new approach to their synthesis has been developed, which is based on an enantioselective partial intramolecular [2 + 2 + 2] cycloaddition between α,ω-diynes and nitriles[6] or alkynes.[7,8] Although various transition metals catalyze alkyne cyclotrimerization, it has been difficult to carry out complete

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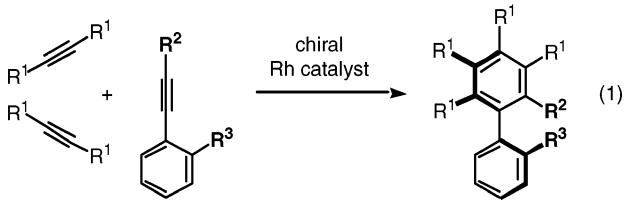
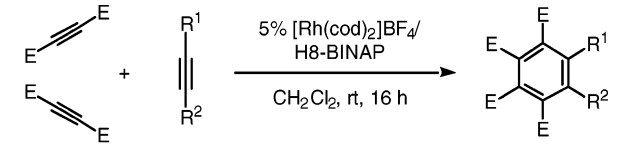
intermolecular reaction of two or three different alkynes with high selectivity.[9] We anticipated that cross-cyclotrimerization of two molecules of symmetrical internal alkynes and one molecule of unsymmetrical internal alkynes, bearing ortho-substituted phenyl at one terminal position, would construct axial chirality during the formation of benzene rings (eq 1). We recently reported a cationic rhodium(I)/H8-BINAP[10] complex-catalyzed complete intermolecular cross cyclotrimerization of terminal alkynes with dialkyl acetylenedicarboxylates.[11,12] In this paper, we describe a cross-cyclotrimerization using internal alkynes and its application to the enantioselective synthesis of axially chiral biaryls.



(1)

We first investigated an intermolecular cross-cyclotrimerization of two different internal alkynes. Screening of various alkynes and Rh(I) complexes revealed that $Rh(I)^+$/H8-BINAP catalyzed chemoselective intermolecular cross-cyclotrimerization of two molecules of diethyl acetylenedicarboxylate (**1a**) and one molecule of internal alkynes (Table 1). Alkyl- (entries 1 and 2), aryl- (entry 3), and alkoxycarbonyl-substituted (entries 4 and 5) internal alkynes were suitable substrates for this reaction. Interestingly, although the reaction of 1,4-dimethoxy-2-butyne (**2f**) proceeded in high yield (entry 6), no reaction was observed in the case of 1,4-diacetoxy-2-butyne (**2g**) (entry 7).

Table 1. Rhodium-Catalyzed Cross-Cyclotrimerization of Internal Alkynes and Diethyl Acetylenedicarboxylate



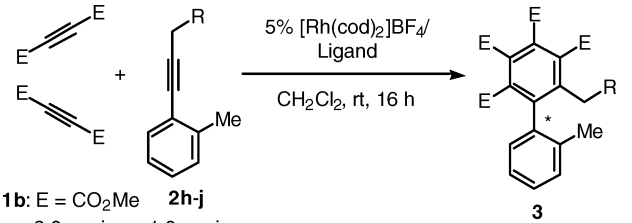
1a: E = CO_2Et 2.0 equiv **2a-g** 1.0 equiv **3**

entry	**2**	R^1	R^2	**3**	yield[a] (%)
1	**2a**	*n*-Pr	*n*-Pr	**3aa**	76
2	**2b**	$(CH_2)_4CH_3$	Me	**3ba**	69
3	**2c**	Ph	Me	**3ca**	68
4	**2d**	Me	CO_2Et	**3da**	82
5	**2e**	Ph	CO_2Et	**3ea**	72
6	**2f**	CH_2OMe	CH_2OMe	**3fa**	82
7	**2g**	CH_2OAc	CH_2OAc	**3ga**	0

[a] Isolated yield.

Next, the reaction of various 2-methylphenyl-substituted internal alkynes **2h**,**i** with dimethyl acetylenedicarboxylate (**1b**) was investigated to construct axial chirality (Table 2).

Table 2. Optimization of Rhodium-Catalyzed Enantioselective Cross-Cyclotrimerization



1b: E = CO_2Me 2.0 equiv **2h-j** 1.0 equiv **3**

entry	**2**	R	ligand	**3**	yield[a] (%)	ee (%)
1	**2h**	H	(*S*)-H8-BINAP	(−)-**3hb**	23	21
2	**2i**	OMe	(*S*)-H8-BINAP	**3ib**	<5	
3	**2j**	OAc	(*S*)-H8-BINAP	(+)-**3jb**	81	89
4	**2j**	OAc	(*R*)-BINAP	(−)-**3jb**	16	77
5	**2j**	OAc	(*S*)-Segphos	**3jb**	<5	

[a] Isolated yield.

In the case of methyl- and methoxymethyl-substituted alkynes **2h** and **2i**, cyclotrimerization of **1b** proceeded rapidly (entries 1 and 2). On the other hand, the use of an acetoxymethyl-substituted alkyne **2j** furnished an axially chiral biaryl in high yield with high enantioselectivity (entry 3). The use of BINAP or Segphos[13] led to poor results (entries 4 and 5) (Figure 1).

The enantioselective intermolecular cross-cyclotrimerization of various acyloxymethyl-substituted alkynes **2j**−**o** and

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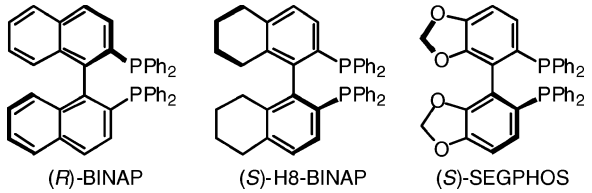
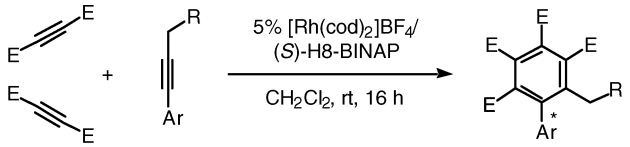


Figure 1. Structures of modified BINAP ligands.

1 was investigated using $Rh(I)^+$/(*S*)-H8-BINAP, and high enantioselectivities were achieved in each reaction (Table 3). The reaction of both acetoxymethyl- and propioxymethyl-

Table 3. Rhodium-Catalyzed Enantioselective Cross-Cyclotrimerization of Internal Alkynes and Dialkyl Acetylenedicarboxylates



1a: E = CO_2Et **2j–p** **3**
1b: E = CO_2Me
2.0 equiv 1.0 equiv

entry	1	2	Ar	R	3	yield[a] (%)	ee (%)
1	**1a**	**2j**	2-MeC_6H_4	OAc	(+)-**3ja**[b]	80	93
2	**1b**	**2k**	2-MeC_6H_4	OCOEt	(+)-**3kb**	73	91
3	**1b**	**2l**	2-EtC_6H_4	OAc	(+)-**3lb**	70	92
4	**1b**	**2m**	2-ClC_6H_4	OAc	(+)-**3mb**	67	84
5	**1b**	**2n**	2-BrC_6H_4	OAc	(*R*)-(−)-**3nb**	61	91
6	**1b**	**2o**	1-naphthyl	OAc	(+)-**3ob**	89	95
7	**1a**	**2p**	1-naphthyl	CH_2OH	(+)-**3pa**	75[c]	96

[a] Isolated yield. [b] (*R*)-H8-BINAP was used. [c] Isolated as the corresponding acetate by treatment with Ac_2O/Et_3N.

substituted alkynes **2j** and **2k** with **1a** and **1b** proceeded in high yield and ee, respectively (entries 1 and 2). Not only 2-methylphenyl-, but also 2-ethylphenyl- (entry 3), 2-chlorophenyl- (entry 4), 2-bromophenyl- (entry 5), and 1-naphthyl-substituted (entry 6) alkynes were suitable substrates in this process. Interestingly, although the reaction of an acetoxyethyl-/1-naphthyl-substituted alkyne with **1a** proceeded in low yield and ee (20%, 28% ee), the reaction of a hydroxyethyl-/1-naphthyl-substituted alkyne **2p** with **1a** proceeded in high yield and ee (entry 7). The absolute configuration of (−)-**3nb** was determined to be *R* by anomalous dispersion method (Figure 2).

Scheme 1 depicts a plausible mechanism of the selective formation of (*R*)-(−)-**3nb**. Chemo- and enantioselectivity are determined by preferential formation of metallacycle **A**

(14) Indeed, in the cross cyclotrimerization shown in Table 3, starting materials **2** and homo-cyclotrimerization products of **1** were isolated other than the desired cross-cyclotrimerization products.

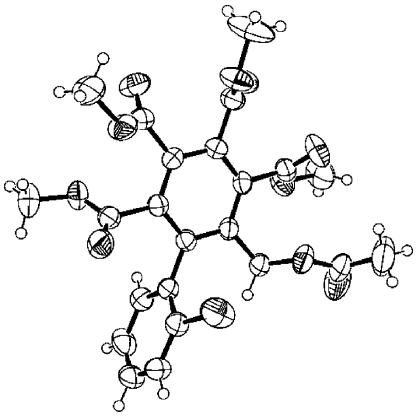
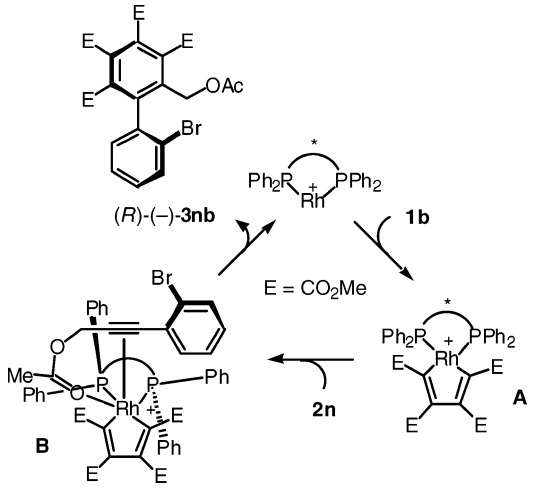


Figure 2. ORTEP diagram of (*R*)-(−)-**3nb**.

followed by the coordination of **2n** to form complex **B**, due to avoidance of the steric interaction between Br atom of **2n** and PPh_2 group of (*S*)-H8-BINAP. Reductive elimination of rhodium gives (*R*)-(−)-**3nb** and regenerates the rhodium catalyst.[14]

Scheme 1



In conclusion, we have developed a rhodium-catalyzed enantioselective complete intermolecular cross cyclotrimerization of internal alkynes for the synthesis of axially chiral biaryls. Detailed mechanistic study and expansion of the scope are underway in our laboratory.

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Supporting Information Available: 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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