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Enantioselective Synthesis of C_2-Symmetric Spirobipyridine Ligands through Cationic Rh(I)/Modified-BINAP-Catalyzed Double [2 + 2 + 2] Cycloaddition

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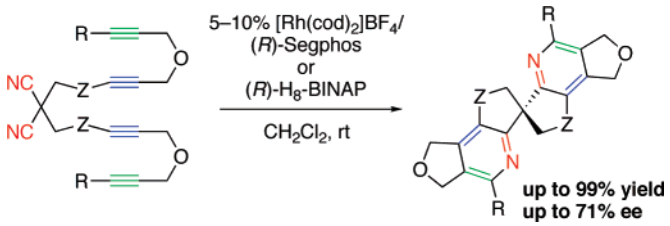
ABSTRACT



Enantioenriched C_2-symmetric spirobipyridine ligands were efficiently synthesized through a cationic rhodium(I)/(*R*)-Segphos or (*R*)-H$_8$-BINAP complex-catalyzed enantioselective intramolecular double [2 + 2 + 2] cycloaddition of bis-diynenitriles.

C_2-Symmetric spiranes having stable axial chirality are valuable structures for efficient chiral ligands because heteroatoms containing chiral spiranes easily form well-defined chelate complexes with many metals.[1−3] Chan, Jiang, and co-workers synthesized the spirophosphinite ligands through phosphinylation of enantiopure spiro[4.4]nonane-1,6-diol.[1] Zhou and co-workers synthesized the chiral spirophosphine ligands through phosphinylation of enantiopure 1,1′-spirobiindane-7,7′-diol.[2] Sasai and co-workers synthesized the chiral spiro ligands bearing nitrogen heterocycles through double annulation reaction followed by separation of diastereomers and/or enantiomers.[3] However, a catalytic enantioselective synthesis of C_2-symmetric spiranes is scarce.[4] A novel catalytic enantioselective synthesis of a C_2-symmetric spirane, 1,1′-spirobi(indan-3,3′-dione), was developed by Hashimoto and co-workers through a rhodium(II)-catalyzed double intramolecular C−H bond insertion.[4a] On the other hand, Saá and co-workers developed an elegant approach to spirobipyridine ligands, which is based on a cobalt(I)-catalyzed double [2 + 2 + 2] cycloaddition of bis-alkynenitriles with monoalkynes, although the synthesis

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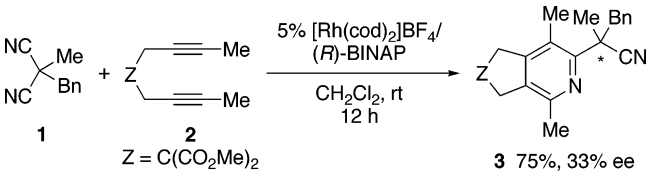
provides racemates and the product yields are not sufficient (6−33% yields).[5] They also demonstrated that a racemic C_2-symmetric spirobipyridine ligand can quantitatively coordinate to $[Cu(CH_3CN)_4]PF_6$, which represents the potential utility of chiral spirobipyridine ligands for asymmetric catalysis.[5]

Our research group first demonstrated that cationic rhodium(I)/modified-BINAP complexes can efficiently catalyze both inter- and intramolecular [2 + 2 + 2] cycloaddition of various unsaturated compounds with high chemo-, regio-, and enantioselectivities.[6,7] Recently, we have applied these catalysts to [2 + 2 + 2] cycloaddition involving nitriles leading to substituted pyridines,[7h,8−13] and the work was further extended to the axially chiral bipyridine synthesis through double [2 + 2 + 2] cycloaddition.[7f,14] In this communication, we describe an enantioselective synthesis of C_2-symmetric spirobipyridine ligands through a cationic rhodium(I)/modified-BINAP complex-catalyzed double [2 + 2 + 2] cycloaddition.

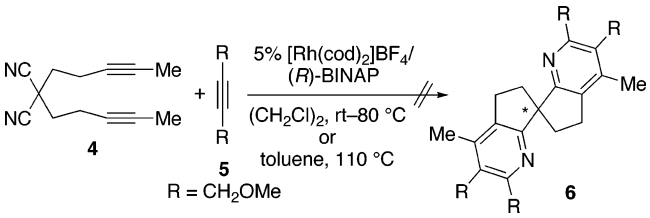
We have already reported that the reaction of substituted malononitrile **1** with 1,6-diyne **2** in the presence of 5% $[Rh(cod)_2]BF_4$/(*R*)-BINAP selectively afforded the corresponding enantioenriched monopyridine **3** having a quaternary stereocenter without the formation of a bipyridine (Scheme 1).[7h]

Scheme 1



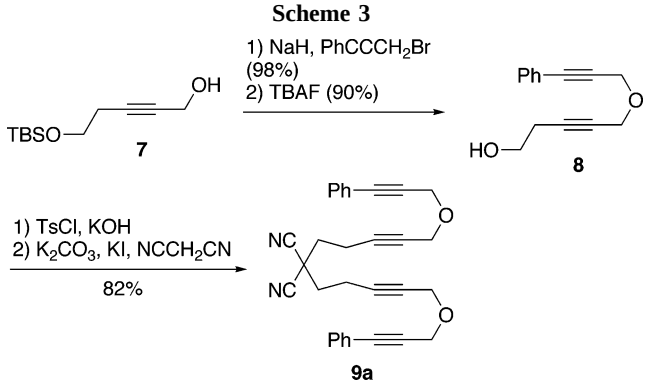
This successful enantioselective construction of a quaternary stereocenter prompted our investigation into a chiral spirobipyridine synthesis. First, we applied the above-mentioned catalyst to intermolecular double [2 + 2 + 2] cycloaddition of bis-alkynenitrile **4** with monoalkyne **5**, but spirobipyridine **6** was not obtained at all and **4** was recovered even at elevated temperature (Scheme 2).[15]

Scheme 2



Next, we attempted the intramolecular double [2 + 2 + 2] cycloaddition of bis-diynenitriles **9**, which can be readily prepared starting from known protected alkyne diol **7**[16] (Scheme 3). Etherification of **7** followed by desilylation

Scheme 3



furnished diyne monool **8**. Dialkylation of malononitrile with the corresponding tosylate of **8** furnished bis-diynenitrile **9a**, possessing a phenyl at each alkyne terminus, in high yield.

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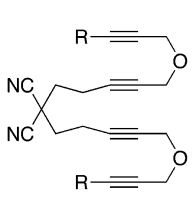
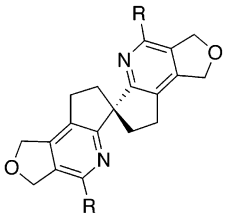
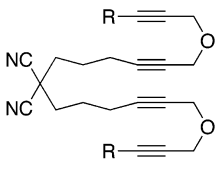
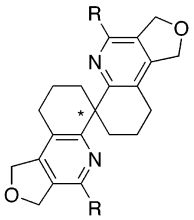
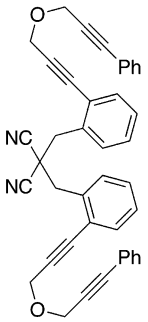
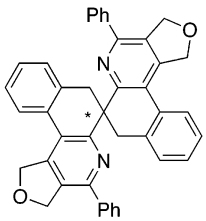
Table 1. $Rh(I)^+$/(*R*)-Segphos or (*R*)-H_8-BINAP Complex-Catalyzed Enantioselective Double [2 + 2 + 2] Cycloaddition of Bis-diynenitriles **9a**−**h**[a]

entry	substrate (**9**)	product (**10**) yield (%)[b]	ee (%)
			
1	R = Ph (**9a**)	99 (**10a**)	64
2[c]	R = 4-ClC_6H_4 (**9b**)	89 (**10b**)	71 (*S*)
3[c]	R = 4-MeOC_6H_4 (**9c**)	85 (**10c**)	62
4	R = Me (**9d**)	98 (**10d**)	49
5	R = H (**9e**)	70 (**10e**)	47
			
6	R = Ph (**9f**)	90 (**10f**)	45
7	R = Me (**9g**)	98 (**10g**)	40
			
8	(**9h**)	99 (**10h**)	18

[a] Reactions were conducted using $[Rh(cod)_2]BF_4$/ligand (0.01 mmol, 10 mol %), **9** (0.10 mmol), and CH_2Cl_2 (1.0 mL) at rt for 16−24 h. Ligand: (*R*)-Segphos (entries 1−3 and 6), (*R*)-H_8-BINAP (entries 4, 5, 7, and 8). [b] Isolated yield. [c] Catalyst: 5 mol %.

Fortunately, the intramolecular double [2 + 2 + 2] cycloaddition of bis-diynenitrile **9a**, catalyzed by 10% $[Rh(cod)_2]BF_4$/modified-BINAP, proceeded to give the expected C_2-symmetric spirobipyridine **10a** in almost quantitative yield.[15] Although the reaction proceeds intramolecularly, a diluted reaction condition or a slow addition is not necessary. The highest enantioselectivity was achieved by using (*R*)-Segphos [(4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine)][17] as a ligand (Table 1, entry 1).[18] The enantiomeric excess is dependent on the electronic nature of aromatic substituents: an electron-withdrawing group furnished higher selectivity than did an electron-donating group (entries 2 and 3). Not only aryl-substituted bis-diynenitriles but methyl-substituted and terminal bis-diynenitriles could also participate in this process by using (*R*)-H_8-BINAP [2,2′-bis-(diphenylphosphino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl][19] as a ligand (entries 4 and 5). Furthermore, C_2-symmetric spirobipyridines **10f**−**h**, possessing a six-membered spiro skeleton, could be synthesized from bis-diynenitriles **9f**−**h** in high yields using (*R*)-Segphos or (*R*)-H_8-BINAP as a ligand, although lower enantioselectivities were observed (entries 6−8). Enantiopure (−)-**10b** was readily obtained by recrystallization from CH_2Cl_2−pentane, and the absolute configuration was determined to be *S* by the anomalous dispersion method (Figure 1).

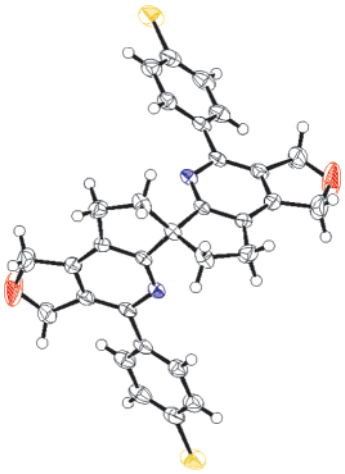


Figure 1. ORTEP diagram of C_2-symmetric spirobipyridine (*S*)-(−)-**10b**.

Scheme 4 depicts a plausible mechanism for the selective formation of (*S*)-(−)-**10b**. Enantioselectivity is determined by preferential formation of metallacycle **A**, due to avoidance

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(14) Synthesis of bipyridines and terpyridines by transition-metal-catalyzed [2 + 2 + 2] cycloadditions: Co(I): (a) Varela, J. A.; Castedo, L.; Saà, C. *J. Org. Chem.* **1997**, *62*, 4189. (b) Varela, J. A.; Castedo, L.; Saà, C. *J. Am. Chem. Soc.* **1998**, *120*, 12147. (c) Varela, J. A.; Castedo, L.; Maestro, M.; Mahia, J.; Saà, C. *Chem.—Eur. J.* **2001**, *7*, 5203. Ru(II): see refs 11k and 11n.

(15) Recently, Yamamoto and co-workers reported that a cyanoalkyne failed to react with 1-hexyne intermolecularly in the presence of [Cp*RuCl(cod)] catalyst, but intramolecular [2 + 2 + 2] cycloadditions of cyanodiynes proceeded to give tricyclic pyridines in the presence of the same Ru catalyst, although a diluted reaction condition or a slow addition is necessary. See ref 11n.

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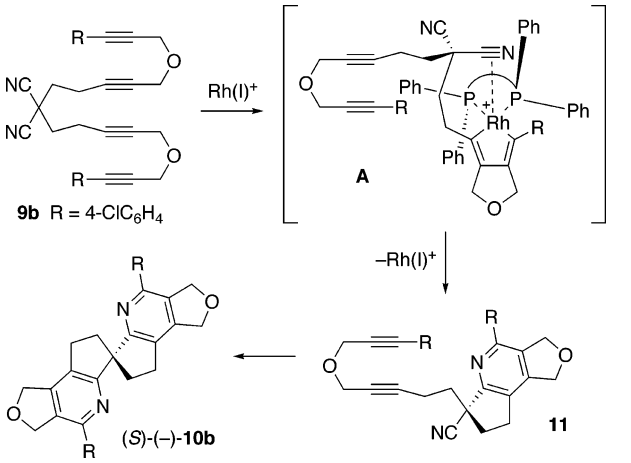
(17) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(18) Results with other BINAP-type ligands: (*R*)-BINAP 58% ee, (*R*)-tol-BINAP 56% ee, (*R*)-xyl-BINAP 51% ee, (*R*)-H_8-BINAP 60% ee.

(19) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1991**, *32*, 7283.

Scheme 4



of the steric interaction between a cyano group of **9b** and the PPh_2 groups of (*R*)-Segphos. Insertion of the cyano group followed by reductive elimination of rhodium gives monoannulation product **11** and regenerates the rhodium catalyst.[20] A subsequent intramolecular [2 + 2 + 2] cycloaddition of **11** provides the expected C_2-symmetric spirobipyridine (*S*)-(−)-**10b**.

In conclusion, we have developed a cationic rhodium(I)/modified-BINAP complex-catalyzed enantioselective intramolecular double [2 + 2 + 2] cycloaddition of bis-diynenitriles leading to enantioenriched C_2-symmetric spirobipyridine ligands. Further applications of the cationic rhodium(I)/modified-BINAP complex-catalyzed enantioselective double [2 + 2 + 2] cycloadditions to the synthesis of various chiral spiro ligands are underway in our laboratory.

Acknowledgment. We thank Takasago International Corporation for the gift of modified-BINAP ligands. This work was partly supported by Kurata Memorial Hitachi Science and Technology Foundation.

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

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(20) Because the first annulation and the second annulation proceed simultaneously, the monoannulation product **11** could not be isolated.