# One-Step Synthesis of Spiropyridines, a Novel Class of C2-Symmetric Chiral Ligands, by Cobalt(I)-Catalyzed [2 + 2 + 2] Cycloadditions between Bis-Alkynenitriles and Alkynes†

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# One-Step Synthesis of Spiropyridines, a Novel Class of $C_2$-Symmetric Chiral Ligands, by Cobalt(I)-Catalyzed [2 + 2 + 2] Cycloadditions between Bis-Alkynenitriles and Alkynes†

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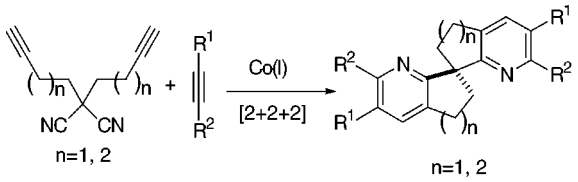
## ABSTRACT




**Spiropyridines, a novel series of $C_2$-symmetric ligands, can be obtained in moderate yields by means of Co(I)-catalyzed double cocyclization between bis-alkynenitriles and alkynes. This one-step method allowed the first synthesis of the interesting 7,7′- and 8,8′-spyropyridines from acyclic precursors.**

The rational design and synthesis of novel chiral ligands for catalysis of asymmetric reactions is currently a major focus of attention in synthetic organic chemistry.[1] Biaryls, most notably 1,1′-binaphthalene phosphane derivatives, occupy a prominent position among $C_2$-symmetric chiral auxiliaries and ligands for asymmetric synthesis.[1] By contrast, spiranes, which also have axial chirality[2] and possess a quaternary center that makes their racemization virtually impossible, have scarcely been used in ligand design.[3] In addition, the major rigidity of its framework compared to that of the biaryls means that any conformational change must necessarily involve distortion of the entire molecule, not merely rotation about a single bond.[3] This latter property is a potentially useful attribute of chiral catalysts (since it should minimize the number of possible conformations of the catalytic species) and also makes spiranes promising building

† Initial results were presented at OMCOS 10, Versailles, July 1999.

(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993.

(2) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 1138−1142.

(3) (a) SpirOP ligands: Hu, W.; Yan, M.; Lau, C.; Yang, S. M.; Chan, A. S. C.; Jiang, Y.; Mi, A. *Tetrahedron Lett* **1999**, *40*, 973−976 and references therein. (b) Spinol ligands: Birman, V. B.; Rheingold, A. L.; Lam, K. *Tetrahedron: Asymmetry* **1999**, *10*, 125−131 and references therein.

(4) Spirosilanes: Tamao, K.; Nakamura, K.; Ishii, H.; Yamaguchi, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 12469−12470.

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(6) Tour, J. M. *Chem. Rev.* **1996**, *96*, 537−553.

(7) For pioneering work on the synthesis of pyridines by Co(I)-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Wakatsuki, Y.; Yamazaki, H. *J. Chem. Soc., Dalton Trans.* **1978**, 1278−1282 and references therein. (b) Bönnemann, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 505−515 and references therein. (c) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539−556 and references therein.

(8) For synthesis of bipyridines and terpyridines using Co(I)-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Varela, J. A.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **1998**, *120*, 12147−12148. (b) Varela, J. A.; Castedo, L.; Saá, C. *J. Org. Chem.* **1997**, *62*, 4189−4192.

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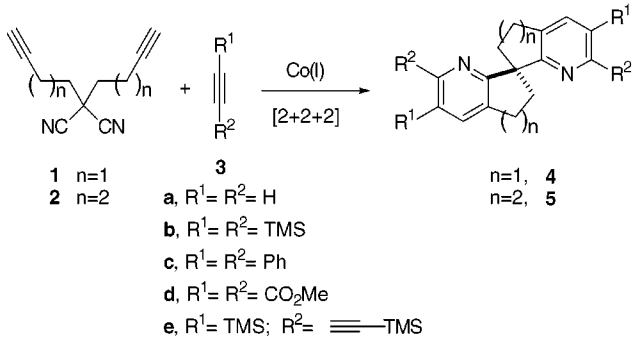
blocks[4] for the construction of chiral macromolecules such as metallacyclic polygons and polyhedra[5] and polymers.[6]

In this paper we report a one-step synthesis of the novel $C_2$-symmetric spirocyclic 7,7′- and 8,8′-bicycloalka[*b*]pyridines (**4** and **5**), hereafter 7,7′-, 8,8′-spiropyridines, respectively, by Co(I)-catalyzed [2 + 2 + 2] cycloaddition[7] between bis-alkynenitriles (malononitriles **1** and **2**) and alkynes **3** (Schemes 1).[8]

**Scheme 1.** Co(I)-Catalyzed Double Cocyclization between Bis-Alkynenitriles **1** and **2** and Alkynes **3**




The bis-alkynenitriles **1** and **2** were easily prepared by dialkylation of malononitrile with tosylates of the corresponding alkyn-1-ols.[9] Gratifyingly, we found that double cocyclization between bis-alkynenitrile **1** and acetylene (**3a**), catalyzed at 2.3 bar[10] by 30% $CpCo(COD)$[11] in toluene,[12] took place in a 32% yield to give the desired (±)-7,7′-spiropyridine **4a**.[13] Dipyridine **6** was also obtained, in 14% yield, as a byproduct originated by multiple cocyclization (Figure 1). The $^1$H NMR spectrum of **4a** showed a

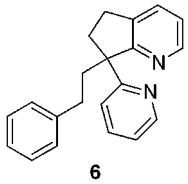



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**Figure 1.**

characteristic series of four well-resolved multiplets corresponding to each one of the diastereotopic aliphatic hydrogens of the molecule. The two enantiomers of **4a** were easily separated by HPLC using a Chiralcel OJ column.[14] It is remarkable that it was possible to assemble the skeleton of this interesting novel type of $C_2$-symmetric spirocyclic compound in only one step from acyclic starting materials.

In an effort to improve the yield of **4a** and minimize the amount of byproduct, we used milder conditions (atmospheric pressure and room temperature) and the more active catalyst $CpCo(C_2H_4)_2$,[15] but unfortunately, the reaction yield was lower (**4a**, 21%; **6**, 11%).[16] When typical Co(I)-catalyzed cycloaddition conditions were used (irradiation, in a sealed tube, of a boiling toluene solution of **1** saturated with acetylene and containing 30% $CpCo(CO)_2$ as catalyst),[8] the yield of **4a** was even worse (7%). To explore the versatility of the above method for preparing other 7,7′-spiropyridines, we performed $CpCo(CO)_2$-catalyzed [2 + 2 + 2] cycloadditions between bis-alkynenitrile **1** and other alkynes. Double cocyclization between **1** and bis(trimethylsilyl)acetylene (**3b**, used as cosolvent) produced a 33% yield of the expected (±)-7,7′-spiropyridine **4b**. Irrespective of the electronic nature of the substituents, when the quantity of alkyne partner was reduced to 2 or 3 equiv, the yield of the reaction dropped: under these conditions diphenylacetylene (**3c**), DMAD (**3d**), and 1,4-bis(trimethylsilyl)-1,3-butadiyne (**3e**) afforded the (±)-7,7′-spiropyridines **4c**, **4d**, and **4e** in 9%, 7%, and 8% yields, respectively.[17] Similar results were found when the bis-alkynenitrile **2** was used: double cocylization between **2** and **3b** (as cosolvent) or **3e** (2 equiv) gave (±)-8,8′-spiropyridines **5b** and **5e** in 32% and 6% yields, respectively.[18] The moderate or low yields of these reactions may be due to the *gem*-dinitrile unit of malononitriles **1** and **2** reducing the donor character of the nitrile, disfavoring stabilization of the cobaltacycle intermediate.[19]

Finally, our first test of formation of coordination complexes with 7,7′-spiropyridines was promising since (±)-**4a** almost quantitatively gave the tetracoordinate complex $[Cu^IL_2]$ as a diastereomeric mixture (**7**, obtained as pale yellow crystalls of the hexafluorophosphate salt) when $[Cu^I(CH_3CN)]PF_6$ was added to solution of (±)-**4a** in $CH_2Cl_2$ at room temperature (Figure 2). A salient feature of its

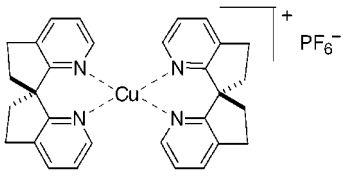


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**Figure 2.**

$^1$H NMR spectrum in $CDCl_3$ is the deshielding of the hydrogen para to the nitrogen, which appears at 7.6 ppm vs 7.4 ppm in the free ligand.

To sum up, we have developed the first method for synthesizing a novel series of $C_2$-symmetric ligands, the

(9) For preparation of bis-alkynenitrile **1** it was necessary to add 2.5 equiv of NaI. See Supporting Information.

(10) Other pressures, whether higher (5.3 bar) or lower (1.2 bar), gave poorer yields of **4a** (20% and 9%, respectively).

(11) King, R. B.; Treichel, P. M.; Stone, F. G. A. *J. Am. Chem. Soc.* **1961**, *83*, 3593−3597.

(12) A similar set of conditions has previously been used to prepare pyridines from nitriles and acetylene. See: Chelucci, G. *Tetrahedron: Asymmetry* **1995**, *6*, 811−826.

(13) All new compounds gave satisfactory analytical and spectroscopic data.

spiropyridines, from acyclic precursors. This one-step method consists of Co(I)-catalyzed double cocyclization between bis-alkynenitriles and alkynes. Studies of the coordination behavior of these ligands are in progress and will be reported on in due course.

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**Supporting Information Available:** Experimental procedures and characterization data for all new compounds. $^1$H and $^{13}$C NMR spectra of **4a**, **5b′**, and **5e**, $^1$H NMR of **7**, CD spectra of (+) and (−) **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) HPLC: $t_R$ first enantiomer, 17.50 min; $t_R$ second enantiomer, 22.20 min (Daicel Chiralcel OJ, 90:10 hexane/2-propanol, 0.5 mL/min). First enantiomer: CD (EtOH) $\lambda$ (nm): 212 (+), 258 (+), 276 (−), 281 (−). Second enantiomer: CD (EtOH) $\lambda$ (nm): 212 (−), 258 (−), 276 (+), 281 (+).

(15) The catalyst was prepared as described by Cammack, J. K.; Jalisatgi, S.; Matzger, A. J.; Negrón, A.; Vollhardt, K. P. C. *J. Org. Chem.* **1996**, *61*, 4798−4800.

(16) Both **4a** and **6** appeared at the beginning of the reaction. To consume all starting material, a substoichiometric amount of catalyst (60%) was necessary.

(17) See Supporting Information for experimental details.

(18) After purification steps, desilylation of TMS in α of **5b** occurred to give **5b′** ($R_2$ = H). See ref 8 and Supporting Information.

(19) Naiman, A.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 708−709.