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# A New Strategy for the Synthesis of Axially Chiral Biaryl Compounds

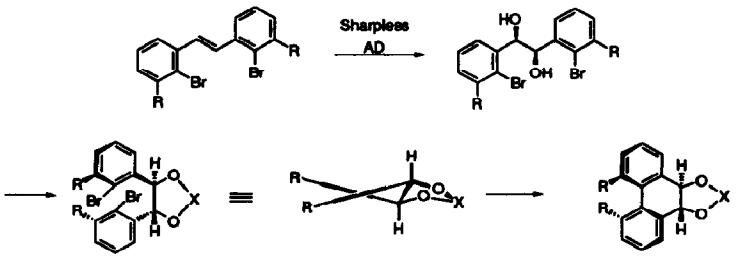
Viresh H. Rawal,* Alan S. Florjancic,[1] and Surendra P. Singh

*Department of Chemistry, The Ohio State University*
*Columbus, OH 43210*

**Abstract:** Axially chiral compounds can be synthesized in high atropisomeric purity by aryl coupling of a conformationally locked dihydroxy-stilbenoids, which are readily available via Sharpless asymmetric dihydroxylation of olefin precursors.

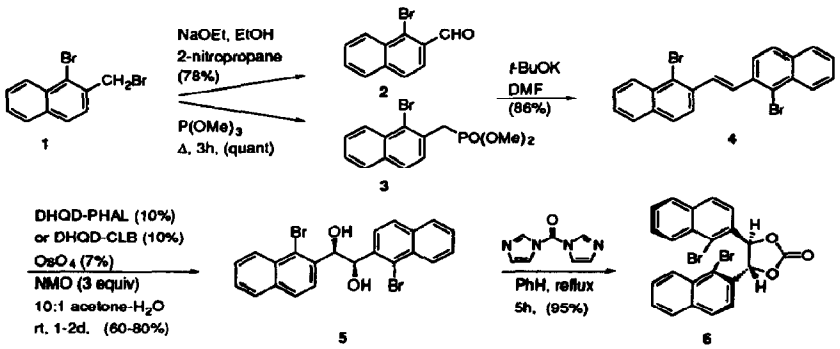
Chiral biaryl units are present in a wide range of compounds,[2] from natural products such as the ellagitannins[3] to chiral stoichiometric reagents and chiral catalysts. Despite their prevalence and importance, there are few routes for the direct synthesis of such axially chiral compounds.[2] Generally, scalemic biaryls are prepared either through resolution or by synthetic routes that use a stoichiometric chiral auxiliary to induce asymmetry.[4, 5] For the past two years we have been working on a new strategy that would allow the use of a catalytic reaction to introduce the axial chirality of biaryls (Scheme).[1, 6, 7] Our strategy takes advantage of two key processes: (1) a highly efficient catalytic reaction, the Sharpless asymmetric dihydroxylation (AD),[8] to introduce chirality into a planar stilbenoid precursor, and (2) an intramolecular aryl coupling reaction to translate the carbon-centered chirality into axial chirality.[9] Examination of molecular models and computer minimizations suggested that tying up the diol with a short tether would predispose the molecule to form primarily one of the two atropisomers.

**Scheme**

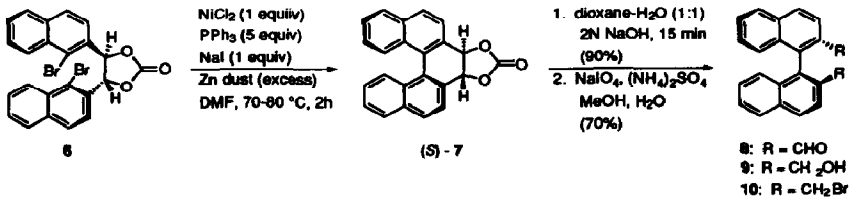


The strategy was examined through the synthesis of a chiral binaphthyl, one of the most frequently utilized biaryl. Both precursors to the required stilbenoid **4** were available from dibromide **1**. Oxidation of the bromide under the Hass-Bender conditions gave 1-bromo-2-naphthaldehyde in 70-80% yield.[10] The phosphonate was prepared in quantitative yield under standard Arbuzov conditions. The Wittig reaction between aldehyde **2** and phosphonate **3** in DMF using *t*-BuOK as the base afforded the desired *trans*-stilbenoid **4** in ~80% yield, mp 144-147 °C, after recrystallization from 10:1 hexane:ethyl acetate.

Installation of chirality into the planar stilbenoid required the examination of several variations of Sharpless' AD conditions. The osmylation product was obtained in only low yield using the most recently reported conditions, presumably because of the low solubility of the polyaromatic substrate in *t*-BuOH/$H_2O$, the recommended solvent system.[11] Success was achieved with Sharpless' older conditions. Treatment of the olefin with $OsO_4$ (7 mol%), DHQD ligand (10 mol %), and NMO (3 equiv) in 10:1 acetone-water mixture afforded the desired diol in 60-80% yield, after chromatography. Chiral HPLC analysis[12] of **5** showed the reaction had proceeded in 92% ee with DHQD-CLB ligand, and in 95% ee with DHQD-PHAL ligand. The purity was improved to >99% ee by a single recrystallization from acetone-hexanes. By analogy with the numerous examples studied by Sharpless, the absolute configuration of **5** is expected to be *R, R*.[13] An analysis of the two intramolecular coupling products shows that the formation of both atropisomers is feasible, with one having the hydroxyls in a diaxial arrangement and the other, diequatorial. Since all remaining carbons are $sp^2$ hybridized, steric factors were not expected to greatly favor one over the other. High chirality transfer was, however, expected after locking the diol into a ring, which would minimize the available conformations during the coupling step. Treatment of diol **5** with carbonyldiimidazole afforded the locked biaryl **6** in nearly quantitative yield.[14]



Carbonate **6** was surprisingly reluctant to undergo an intramolecular coupling reaction under Ullmann-type conditions. Success was, however, achieved using Semmelhack's Ni(0) catalyst system, which has been reported to be a mild, high-yielding alternative to the Ullmann reaction for intramolecular couplings.[15] The required catalyst was prepared in situ by heating to 60 °C a mixture of $NiCl_2$ (1.1 equiv), $PPh_3$ (5.5 equiv), NaI (1.0 equiv), and excess Zn dust (10 equiv) for 1h. In the presence of this catalyst system, the desired coupling was accomplished in 33% yield.[16] The carbonate group was readily removed by stirring **7** with dilute NaOH in aqueous dioxane to afford the corresponding diol. Treatment of this cyclic diol with periodate gave dialdehyde **8**, which was reduced with $NaBH_4$ to yield binaphthalene-diol **9**. Chiral HPLC analysis of **8** and **9** showed them to be single atropisomers (>97% ee).[12] For comparison, authentic samples of racemic and optically pure **8** and **9** were synthesized. Racemic and optically pure dibromides **10**[17] were oxidized using the Hass-Bender conditions to the dialdehydes, which were then reduced. Based on comparison with authentic samples, the axial chirality of **7**, **8**, and **9** was confirmed to be *S* (shown), as expected from the original analysis.




In conclusion, we have developed a new strategy for the synthesis of axially chiral biaryl compounds. The strategy takes advantage of a catalytic process, the Sharpless asymmetric dihydroxylation, to introduce chirality into a planar, prochiral stilbene derivative. After tethering the hydroxyl groups to restrict the available conformations of the two aryl groups, this chirality is translated into axial chirality by a transition metal-mediated aryl coupling reaction. We are applying this novel use of chirality transfer to the synthesis of other axially chiral molecules, such as biaryl natural products and helical molecules.

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