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The Synthesis of a Useful Chiral Biaryl Catalyst. An Oxazoline-Mediated Ullmann Reaction.

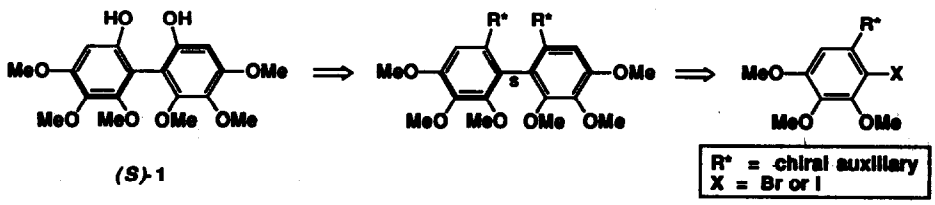
Todd D. Nelson and A. I. Meyers*

Department of Chemistry, Colorado State University, Fort Collins, CO 80523 U.S.A.

Summary: *A rapid synthesis of the enantiomerically pure biaryl catalyst (S)-1 was accomplished by a stereoselective Ullmann reaction (Scheme 1).*

Enantiomerically pure, C_2 symmetric biaryls have been used extensively in asymmetric organic synthesis.[1,2] Among the more pragmatic processes leading to these biaryls is the nucleophilic aromatic substitution of an aryl Grignard to an aryl oxazoline.[3] We have previously taken advantage of this coupling strategy in the synthesis of biphenyl diol (*S*)-**1**,[4] which has functioned as a chiral catalyst in the asymmetric reduction of unsymmetrical ketones.[5] We reasoned that since the diol was a C_2 symmetric biaryl, it might be accessible more efficiently by an aryl-aryl coupling between two identical aromatic units (**Scheme 1**).

Scheme 1



(*S*)-**1**

To date, only a single example of the *intermolecular asymmetric Ullmann* reaction has been disclosed.[6] Poor optical yields (1.8 - 13% d.e.) were reported using chiral alcohol esters of 1-bromo-2-naphthoic acid.

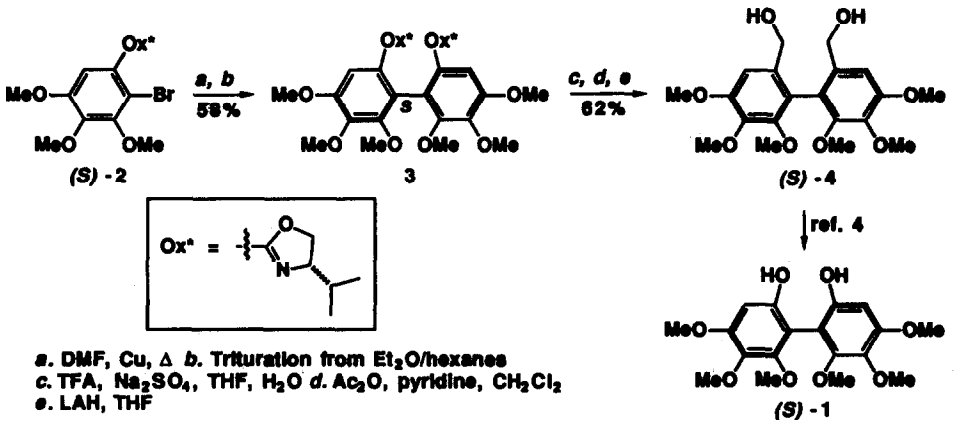
We now describe a successful stereoselective Ullmann reaction, which employs an oxazoline as the chiral controller. Oxazoline (*S*)-**2**, prepared in a simple process[7] from 2-bromo-3,4,5-trimethoxybenzoic acid with L-valinol, was subjected to Ullmann reaction conditions to afford bis(oxazoline) **3** as the major atropisomer (**Scheme 2**).[8] The diastereoselectivity for the Ullmann coupling was determined by reducing[3] the crude coupling mixture to the diol **4**. The sign of rotation for the chromatographically purified diol **4** was the same as that of the known diol (*S*)-**4**,[3] thus establishing the absolute stereochemistry about the chiral biaryl axis. In addition, chiral HPLC (Chiracel OD) analysis of crude diol **4** indicated a enantiomeric ratio of 94:6 (S:R).

The reaction mixture from above was found to be contaminated with small amounts of the dehalogenated oxazoline arising from the reduction of (*S*)-**2**, which was readily separated from the atropisomers by silica gel chromatography. The major diastereomer **3** was then obtained in

a 58% yield (trituration with Et_2O/hexane). Reduction of the latter led to enantiomerically pure samples of the known dicarbinol (*S*)-**4**, which was transformed into biphenol (*S*)-**1**, identical in all respects to that previously reported.[4]

This protocol now allows for a convenient preparation of chiral biaryl (and binaphthyl) compounds from easily prepared symmetric aryl precursors. The preparation of other bis(oxazolines) and a discussion of the mechanism of this process will be published in due course.[9]

Scheme 2



a. DMF, Cu, Δ *b*. Trituration from Et_2O/hexanes
c. TFA, Na_2SO_4, THF, H_2O *d*. Ac_2O, pyridine, CH_2Cl_2
e. LAH, THF

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References and Notes

1. For recent reviews on the synthetic applications of C_2 symmetric biaryls see: a) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. b) Narasaka, K. *Synthesis* **1991**, 1. c) Tomioka, K. *Synthesis* **1990**, 541.
2. For recent reviews on the asymmetric syntheses of chiral biaryls see: a) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. b) Bringmann, G.; Walter, R.; Weirich, R. in *Houben Weyl*, E22, C2; in press.
3. For example: Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090.
4. Meyers, A. I.; Meier, A.; Rawson, D. J. *Tetrahedron Lett.* **1992**, *33*, 853.
5. Rawson, D.; Meyers, A. I. *J. Chem. Soc., Chem. Commun.* **1992**, 494.
6. Miyano, S.; Tobita, M.; Suzuki, S.; Nishikawa, Y.; Hashimoto, H. *Chem. Letters* **1980**, 1027.
7. a) For a typical carboxylic acid to oxazoline conversion see: Gant, T. G.; Meyers, A. I. *J. Am. Chem. Soc.* **1992**, *114*, 1010. b) All new compounds were characterized by ^1H and ^{13}C NMR spectroscopy and combustion analysis.
8. A dry flask was charged with 1.11 g (3.1 mmol) of the bromo oxazoline *(S)*-**2**, 1.04 g of Cu powder, and 1.5 mL of DMF under Ar. This was placed in a prewarmed (110°C) sand bath for 3 h. An additional 8.5 mL of DMF were added and the mixture refluxed for 24 h. After cooling, the mixture was diluted with CH_2Cl_2, washed with 4% aq. NH_4OH (3 x 200 mL) and H_2O (100 mL), dried over Na_2SO_4, filtered and the solvent removed. The reduced starting material (higher R_f) was removed from the bis(oxazoline) **3** by radial chromatography (98:2, hexane/Et_3N). Trituration with Et_2O/hexane then afforded 500 mg (0.9 mmol) of the diastereomerically pure bis(oxazoline) **3** (*S*-biaryl axis) as a colorless solid in a 58% yield; mp 81.5-82.5°C, $[\alpha]_D$ -31.8° (c = 3.3, $CHCl_3$);
9. In preliminary experiments, the stereoselectivity leading to bis(oxazoline) **3** appears to be based on thermodynamic considerations (i.e. prolonged heating of the reaction mixture improves the diastereomeric ratio for this coupling process.)

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