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An Asymmetric Synthesis of a C_2 Symmetric Tetrasubstituted Biaryl: 2,2'-Dihydroxy-6,6'-Dimethyl-1,1'-Biphenyl, A Stable Chiral System

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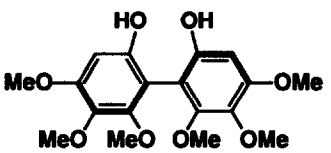
Summary: *An asymmetric synthesis of enantiomerically pure bisphenol (S)-12 was accomplished in 40-50% by an oxazoline mediated biaryl coupling.*

In the preceding paper[1] we reported the preparation of tetrasubstituted, enantiomerically stable biaryls *via* a chiral oxazoline-mediated coupling. Herein, we describe our use of this methodology in the synthesis of C_2 symmetrical bisphenol, (*S*)-**12**. In previous studies from this laboratory,[2] we demonstrated that enantiomerically stable biaryls required at least three ortho substituents to avoid racemization *via* rotation of the internal bond. In our continuing program to reach C_2 symmetric biphenyls, we recently described the hexasubstituted bisphenol **1** and its use as a chiral hydride reagent.[2b,2c] It was, therefore, our intent to prepare in high enantiomeric purity a simpler version of **1**, which hopefully could be accessed in an efficient manner. This disubstituted bisphenol **12** has been previously resolved into enantiomers and utilized as a chiral modifier of metal hydrides.[3] This report represents the first asymmetric route to **12**.



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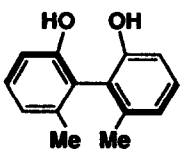
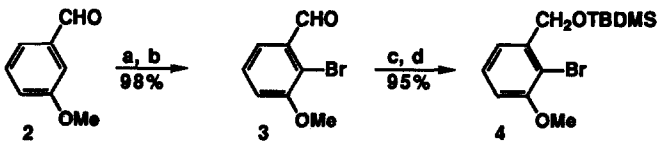


(*S*)-**12**

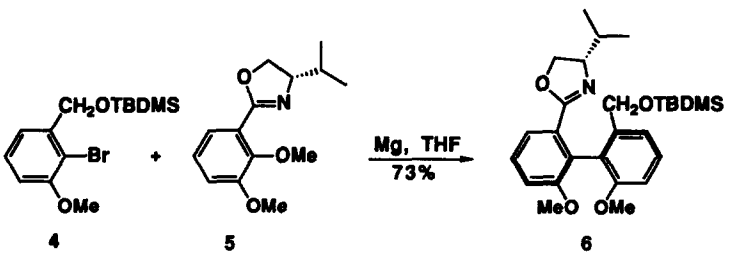
The precursors to the biaryl coupling were prepared as shown in Scheme 1. Starting from *m*-anisaldehyde (**2**) an α-aminoalkoxide-directed lithiation, as developed by Comins,[4] was performed followed by bromination to give **3** in 98% yield. Reduction of the aldehyde with DIBAL followed by protection of the benzylic alcohol as a silyl ether afforded aryl bromide **4** as one of the two components required for the biaryl coupling. The other component, oxazoline (*S*)-**5**, was readily prepared from 2,3-dimethoxybenzoic acid and L-valinol.[5]



a) *n*-BuLi, $HNMeCH_2CH_2NMe_2$, PhLi, benzene, THF b) $BrCF_2CF_2Br$
c) DIBAL-H, THF d) t-$BuMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2

Scheme 1

The coupling of the Grignard reagent of **4** and oxazoline **5** proceeded smoothly to completion in THF at ambient temperature after stirring for 6 h and biaryl **6** was formed as a 93:7 mixture of atropisomers (73% isolated yield).[6] The preceding coupling also occurred at 0° C, resulting in a 95:5 mixture of atropisomers, although the reaction was considerably slower at this temperature.



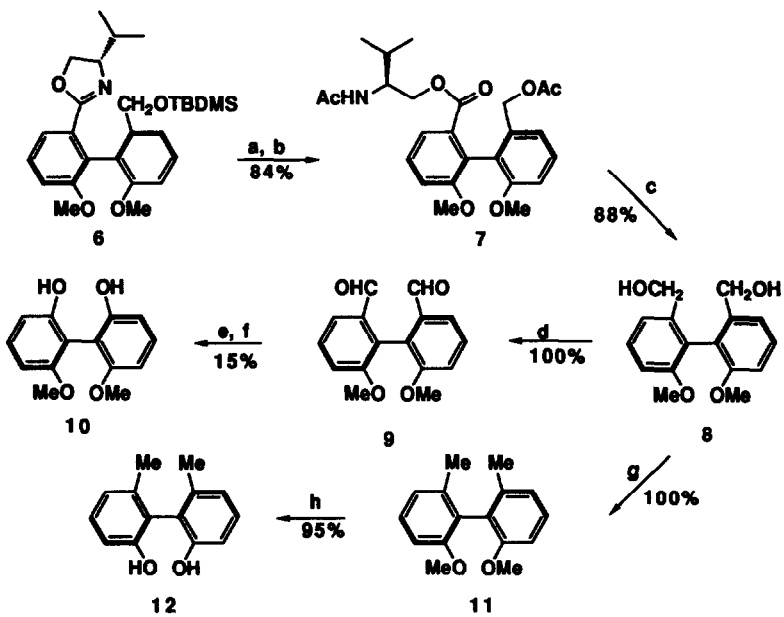
The diastereomeric mixture **6** or the corresponding desilylated alcohol was readily separated and purified using radial chromatography[7] and the chief product was taken on to a series of C_2 symmetrical biaryls as outlined in **Scheme 2**.[8] Thus, biphenyl **6** was converted into the stable diester amide **7** with aqueous trifluoroacetic acid followed by acetylation of the unstable ammonium salt with acetic anhydride.[9] Reduction of **7** with $LiAlH_4$ furnished biphenyl biscarbinol **8** as a single enantiomer which was readily confirmed by a comparison of the ^1H NMR spectrum of the Mosher's ester of **8** with that of racemic material.[10] Due to the sp^3 carbons in both ortho positions, **8** proved to be stable toward racemization when heated at 90° C.

Sarrett oxidation[11] of alcohol **8** gave the 2,2'-diformyl biphenyl **9** in quantitative yield but was found to be much more prone to racemization since the sp^2 hybridized formyl substituents were unable to inhibit aryl-aryl bond rotation. In fact, after heating at 90° C for 30 h **9** lost half of its optical activity. An attempt was made to oxidize the diformyl biphenyl **9** to bisphenol **10** using Bayer-Villiger conditions, analogous to the procedure followed in the synthesis of bisphenol **1**.[2b] However, the desired bisphenol was only formed in 15% yield. The electron donating methoxy substituent in the meta position in **9** causes the rearrangement to proceed away from the desired formate ester which upon hydrolysis would have given bisphenol **10**.[13]

In order to circumvent this problem, the benzylic hydroxyl groups in **8** were easily hydrogenolyzed in the presence of Pd/C and a catalytic amount of TFA. The hydrogenolysis

proceeded under a balloon filled with hydrogen, to afford dimethoxydimethyl biphenyl **11** in quantitative yield. The desired bisphenol **12** was readily obtained in 95% yield after methoxyl cleavage of **11** with BBr_3. Since the classical resolution[14] of **12** has been previously reported, we were able to assign the absolute configuration of **12** prepared herein. The configuration was determined to be S and no racemization was detectable during the conversion of **6** to **12**. Because of this the major atropisomer formed during the biaryl coupling to **6** must have the *S* configuration. These results confirm the proposed pathway for the biaryl coupling as a chelation controlled addition-elimination process.[1]

In summary, we can report a useful stereocontrolled biaryl coupling that allows the synthesis of enantiomerically pure C_2 symmetrical biphenyls.[12] The overall yield of *S*-**12** from oxazoline **5** was 50-55% on a 2 gram scale, and this compares favorably to the 15% overall yield obtained *via* Ullmann coupling-resolution approach described by Kanoh, et al.[14] Application of these chiral biaryls as catalysts in a variety of reactions is currently in progress in our laboratories.[15]



a) Na_2SO_4, TFA, THF, H_2O b) Ac_2O, pyridine, CH_2Cl_2 c) $LiAlH_4$, THF
d) CrO_3, pyridine, CH_2Cl_2 e) MCPBA, $NaHCO_3$, CH_2Cl_2 f) K_2CO_3, MeOH, H_2O
g) Pd/C (10%), H_2, TFA, EtOH h) BBr_3, CH_2Cl_2

Scheme 2

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References and Notes

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5. For a typical carboxylic acid to oxazoline conversion see: Gant, T. G.; Meyers, A. I. *J. Am. Chem. Soc.* **1992**, *114*, 1010.

6. The same diastereomeric ratio was found when the reaction was carried out in refluxing THF.

7. Desilylation of a diastereomeric mixture of TBDMS biphenyl **6** with 2% HF in acetonitrile/water (10%) at room temperature for 1 h yielded the corresponding hydroxymethylene biphenyl which could also be separated by chromatography (silica, hex-EtOAc).

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9. In case of incomplete separation of the diastereomers of **6** (TBDMS biphenyl), another separation can be done at this stage using radial chromatography; this was usually necessary when the coupling reaction was performed on a larger scale.

10. The diastereotopic benzylic protons in the Mosher's ester of **8** provided an excellent probe for determining the enantiomeric purity of **8** when examined using 300 MHz ^{1}H NMR spectroscopy.

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15. Spectral data (all spectra were recorded in $CDCl_3$) and specific rotations for compounds **6-12**. **6**:^{1}H NMR δ -0.05 (s, 6H), 0.71 (d, J = 6.7 Hz, 3H), 0.75 (d, J = 6.7 Hz, 3H), 0.86 (s, 9H), 1.50 (septet, J = 6.7 Hz, 1H), 3.62 (s, 3H), 3.69 (s, 3H), 3.61-3.99 (m, 3H), 4.36 (dd, J = 14 Hz, 2H), 6.77 (d, J = 8.0 Hz, 1H), 7.02 (d, J=8.1 Hz, 1H), 7.18-7.43 (m, 4H).^{13}C NMR δ -5.85, -5.47, 18.18, 18.31, 18.54, 25.91, 32.69, 55.76, 62.74, 70.03, 72.49, 108.93, 112.72, 117.56, 121.82, 122.93, 125.15, 127.96, 128.36, 130.32, 141.55, 156.45, 156.82, 163.68. **7**:^{1}H NMR δ 0.72 (t, J = 6.8 Hz, 6H), 0.99 (m, J = 6.8 Hz, 1H), 1.88 (s, 3H), 1.92 (s, 3H), 3.68 (s, 3H), 3.71 (s, 3H), 3.61-3.71 (m, 1H), 3.92 (dd, J = 3.0 Hz, J = 11.7 Hz, 1H), 4.22 (dd, J = 3.0 Hz, J = 11.7 Hz, 1H), 4.73 (dd, J = 12.7 Hz, 2H), 5.19 (d, J = 9.3 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 7.04-7.11 (m, 2H), 7.30-7.42 (m, 3H), 7.64 (d, J = 7.8 Hz, 1H). ^{13}C NMR δ 19.20, 19.53, 20.73, 23.09, 27.77, 53.04, 55.60, 56.05, 64.45, 65.55, 110.46, 114.60, 119.96, 123.21, 124.54, 126.19, 128.24, 128.99, 132.42, 135.62, 156.83, 156.89, 167.80, 169.60, 170.63. **8**:^{1}H NMR δ 2.64 (s, 2H), 3.67 (s, 6H), 4.19 (dd, J = 11.7 Hz), 2H), 6.93 (d, J = 8.2 Hz), 2H), 7.13 (d, J = 7.5 Hz, 2H), 7.37 (t, J = 7.9 Hz, 2H).^{13}C NMR δ 55.87, 63.27, 110.63, 121.79, 124.23, 129.12, 140.90, 156.63. $[\alpha]_D$ -96.5° (*c* = 1.00, $CHCl_3$); mp 136.0-136.5 °C. **9**:^{1}H NMR δ 3.71 (s, 6H), 7.18-7.66 (m, 6H), 9.64 (s, 2H); ^{13}C NMR δ 56.59, 115.85, 119.71, 124.54, 129.81, 136.14, 143.32, 191.64. $[\alpha]_D$ -291° (*c* = 1.30, $CHCl_3$). **10**: ^{1}H NMR δ 3.70 (s, 6H), 5.00 (s, 2H), 6.55 (d, J = 8.0 Hz, 2H), 6.65 (d, J = 7.9 Hz, 2H), 7.24 (t, [illegible] 19.56, 55.77, 108.31, 122.19, 126.19, 127.87, 138.18, 156.93. $[\alpha]_D$ -53.0° (*c* = 1.00, $CHCl_3$); mp 85.9-86.3° C. **12**: ^{1}H NMR δ 1.99 (s, 6H), 4.66 (s, 2H), 6.86-6.92 (m, 4H), 7.21-7.27 (m, 2H); ^{13}C NMR δ 19.49, 113.16, 119.49, 122.62, 130.15, 138.94, 154.81. $[\alpha]_D$ -60.5° (*c* = 1.00, $CHCl_3$); mp 159.2-159.7 °C (lit.[14] 159-160° C).

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