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A Highly Stereoselective Synthesis of Axially Chiral Biaryls. Application to the Synthesis of a Potential Chiral Catalyst.

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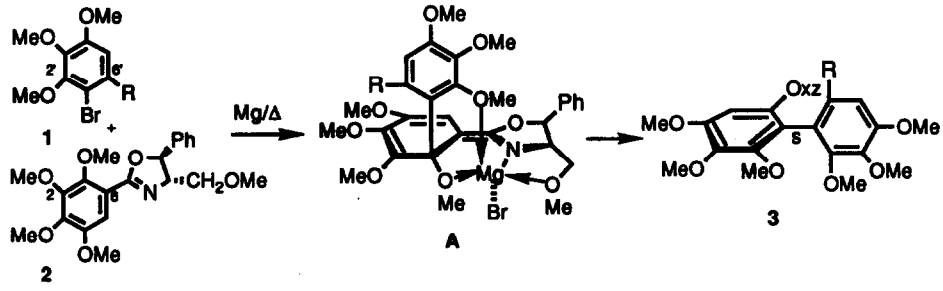
Summary: *Excellent diastereoselectivities (>98:2) have been obtained in the biaryl coupling of 2',6',-disubstituted aryl Grignard reagents* **1** *with aryl oxazolines* **6**, *conveniently synthesised from the optically pure amino alcohols L-valinol and (S)-t-leucinol.*

Axially chiral biaryls are an important feature of many natural products[1] and much effort has been directed in our laboratory towards the synthesis of both biaryls[2] and binaphthyls[3] of high optical purity. One of the most successful approaches to this problem has been through the use of chiral oxazolines[4] derived from (+)-1-methoxy-2-amino-3-phenyl-3-hydroxypropane, and diastereoselectivities of up to 75% de have been achieved in the crucial asymmetric axial C-C bond-forming reaction. The diastereomeric products can usually be separated prior to hydrolytic removal of the oxazoline and judicious choice of ortho substituents allows the integrity of the chiral axis to be maintained through further synthetic steps.[5]

The effect of the 6'-substituent (R) on the diastereoselectivity of the coupling reaction of **1** with **2** (Scheme 1) has recently been described as part of a synthesis of (-)-schizandrin.[2a]

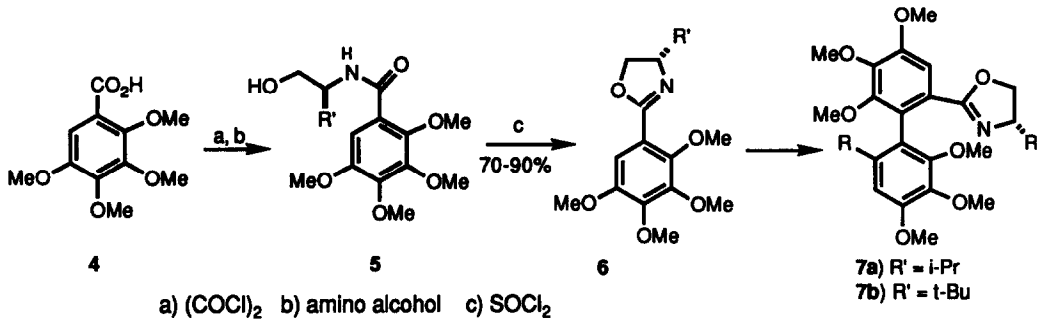


Scheme 1

These coupling reactions were carried out in THF at reflux for 24h . The diastereomeric ratios (S:R) varied from 5:1 (R = CH_3) to 1:5 (R = CH_2OH) and were very dependent on the 6'-substituent. Based on these results and those from a previous study on the asymmetric synthesis of 2,2',6-trisubstituted biphenyls,[5] the coupling is thought to proceed through an addition elimination process (Scheme 1). The magnesium ion is chelated by the aryl oxazoline with the

pendant methoxymethyl group of the oxazoline effectively blocking the lower face from nucleophilic attack. This results in Grignard attack predominantly from the β-face giving the azaenolate intermediate **A**. Free rotation about the newly formed C-C bond allows a combination of steric and electronic effects of the 2' and 6'- substituents to come into play. If the 2'-OMe substituent is a better electron donor to magnesium than the 6'-substituent (as is the case with R = CH_2OMe, $CH_2OTBDMS$ and CH_3) then the (S)-biphenyl product is formed upon collapse of the azaenolate. The selectivity is reversed with a strongly chelating alkoxide group in the 6'-position (R = CH_2O^-) which competes effectively with the 2'-MeO producing the R-product in 90% de, albeit currently in low yield.

We have recently reported the use of amino acid-derived oxazolines in asymmetric C-C bond-forming reactions[6] and planned a study to further enhance both the stereoselectivity and the efficiency of the biaryl coupling reaction. For this reason, the amino acid-derived oxazolines **6a** and **6b**[7] were prepared from 2,3,4,5-tetramethoxybenzoic acid and L-valinol or (S)-t-leucinol in a high yielding and simple process (Scheme 2).[8]



Scheme 2

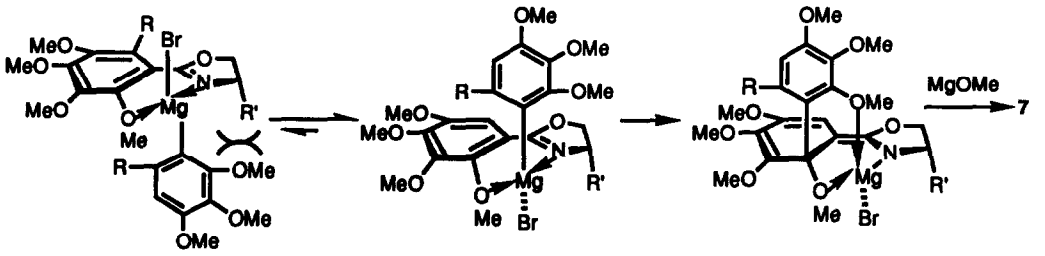
The coupling of **1** and **6** were carried out in THF at reflux (24h for **6a**, 48-60h for **6b**) and the diastereomeric ratios of **7** were determined by HPLC and ^1H NMR. It is clear from the table that the oxazoline couples to **1** with a high degree of stereoselectivity and by adjusting the donor on the 6'-position, either diastereomer of **7** can be reached.

By analogy with the nucleophilic attack of alkyllithiums to naphthyloxazolines[6a] we believe that the chelate-controlled addition begins by the complexation of the Grignard reagent to the lone pair(s) on the oxazoline (Scheme 3). Without a chelating methoxymethyl group on the oxazoline (as in **2**), the steric bulk of R' (^{i}Pr or ^{t}Bu) appears to be sufficient to mask the lower face giving

Table 1

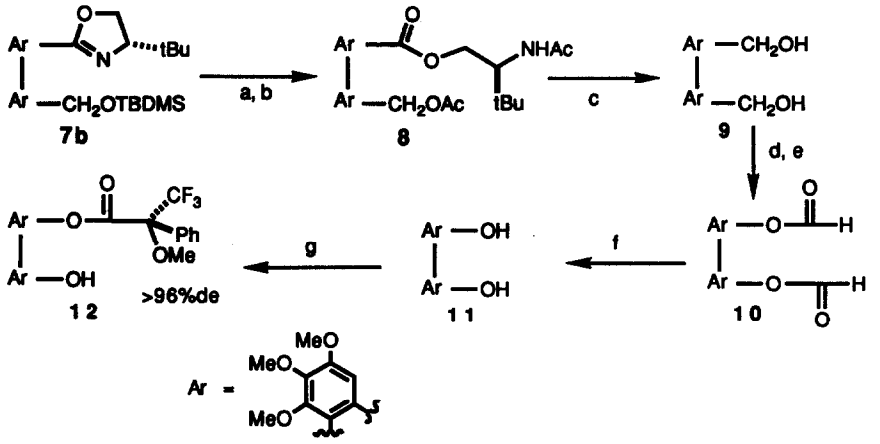
Oxazoline	1, R	Yield 7 %		Diastereomeric Ratio (S:R) 7
	CH_2OMe	56	**7a**	78:22
6a	Me	80		90:10
R' = iPr	CH_2OSiMe_2t-Bu	90		98:2
	CH_2OH	16		5:95
	CH_2OMe	9	**7b**	75:25
6b	Me	75		91:9
R' = tBu	CH_2OSiMe_2t-Bu	60		>98:2

predominantly β-face attack. In almost every case the diastereoselectivity and isolated yields obtained using **6a** and **6b** were superior to those obtained with **2.** In the case of R = $CH_2OTBDMS$, where both the steric and the electronic effects favor the formation of the S-diastereomer, excellent diastereoselectivity was observed for both **6a** and **6b** in the coupling to give **7a** and **7b**, respectively.



Scheme 3

We have carried the coupled product **7b** on to the biphenol **11**,[3] an analogue of the widely used binaphthol.[10] Since the diastereomers present in **7** (98:2) were inseparable by chromatographic means, the mixture was used in the synthesis of **11**. The Mosher's ester [9] of **9** was made using 1eq of Mosher's acid chloride and a comparison of the ^1H and ^{19}F NMR spectra with those of racemic material clearly showed a >98:2 ratio of diastereomers. The dibenzylalcohol **9** could be oxidatively cleaved to the biphenol **11** in a simple 3-step procedure. ^1H and ^{19}F NMR analyses of the mono-Mosher's ester once again indicated a >98:2 ratio of diastereomers showing that the enantiomeric integrity had been maintained during the Bayer-Villiger process. At present, studies are underway to assess biphenol **11** as a chiral catalyst for reduction,[10] the glyoxylate ene reaction,[11] alkylation[12] and the hetero Diels-Alder reaction.[13]



a) Na_2SO_4, TFA, H_2O b) Ac_2O, Pyr 79% c) $LiAlH_4$ 93% d) $(COCl)_2$, DMSO, NEt_3 98% e) mCPBA f) K_2CO_3, MeOH, H_2O 83% g) Mosher's acid chloride, DMAP. NEt_3

Scheme 4

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