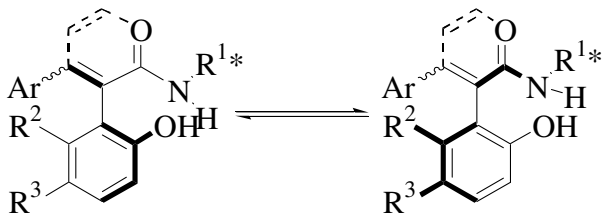
Summary

Axial chirality is a term used to refer to steroisomerism resulting from the non-planar arrangement of four groups in pairs about a chiral axis, so that the resulting spatial arrangement is not superimposable on its mirror image. It is exemplified by allenes and by atropisomers, i.e. conformers resulting from restricted rotation about single bonds, where the rotational barrier is sufficient to allow isolation of the enantiopure species (see below). While the stereoselective synthesis of compounds containing one or more stereogenic centers has emerged as one of the most important fields in chemistry, axial chirality, by contrast, has often been overlooked or treated as an "academic curiosity". This, however, has changed with the recognition that the configuration at a biaryl axis can be a decisive factor in governing the pharmacological properties of a bioactive compound and that axial chirality is the fundamental basis for useful reagents and catalysts in asymmetric synthesis.

In this work, we have developed two main topics:

- ✓ As part of a project aimed at synthesizing new chiral structures to be used as ligands in catalytic asymmetric applications, we decided to investigate the chiral 2-(2-hydroxyaryl)cinnamic amides, which are obtained from the coupling of the corresponding 2-(2-hydroxyaryl) cinnamic acids and a chiral primary amine.[1] These molecules were chosen since they possess several potential sites of diversity (R^1, R^2, R^3, Ar), which allow for the fine-tuning of their steric, electronic and conformational properties:



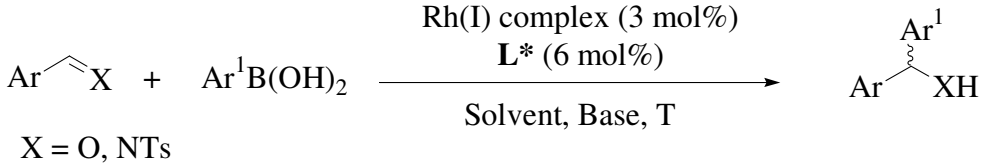
R^1*NH = chiral amine

  In addition, we were also intrigued by the fact that they were structurally reminiscent of biaryl compounds and might display restricted rotation about the

C_2-C_{aryl} bond and, depending on the energetic barrier to rotation, be resolved into two diastereomeric atropisomeric forms.

The synthesis of several differently substituted chiral amides formally derived from a chiral amine and either *E*-2-(2-hydroxyphenyl)cinnamic acid or both *E*- and *Z*-2-(2-hydroxynaphthyl)cinnamic acid was obtained. These molecules display a restricted rotation about the C_2-C_{aryl} bond and, depending on their barrier to rotation, can be isolated in two atropisomeric forms. The barriers to rotation about the C_2-C_{aryl} were measured by dynamic ^{1}H-NMR and were found to to vary between 11.8 and 24.5 kcal mol^{-1}, depending on the substitution. In particular, *E*-2-(2-hydroxynapthyl)cinnamic amides **2.16** displayed a high barrier to rotation ($\Delta G_c^{\ddagger}$ > 24.4 Kcal/mol) and could be isolated as both diastereomerically pure forms at room temperature. The X-ray structure of one *E*-2-(2-hydroxynapthyl)cinnamic amide, (*aR*)-*E*-**2.16a**, was resolved, allowing the determination of the absolute configuration of the chiral axis.

- ✓ As a second project for this thesis work, a small library of chiral monodentate biphenolic and binaphtholic phosphites and phosphoramidites was prepared, and screened in the enantioselective addition of arylboronic acids to aldehydes and *N*-tosylarylimines for the production of diarylmethanol and diarylmethylamines.[2] The ligands were tested either individually or as binary combinations (L_a/L_b 1:1)



Unfortunately, in the case of arylation of aldehydes (X = O in the scheme above) only a few monodentate ligands showed some catalytic activity albeit with a marginal enantioselectivity.

In the addition to *N*-tosylbenzaldimine, good enantiomeric excesses were obtained with binaphtholic phosphoramidite ligands containing a bulky chiral amine. The scope of the substrate and the arylboronic acid was also explored. Good to excellent ee's (76-99%) were also obtained in the arylation of differently substituted N-tosylarylimines, containing either electron-donating or electron-withdrawing

substutents. Electron-rich substrates gave generally higher yields, while a slower addition reaction, associated with lower overall yields, occurred with electron-poor substrates. Electron-rich arylboronic acids gave generally good yields in the addition to N-tosylbenzaldimine, associated with moderate/good ee's.

[1] Marelli, C.; Monti, C.; Galli, S.; Ma sciocchi, N.; Piarulli, U. *Tetrahedron* **2006**, *62*, 8943.
[2] Marelli, C.; Monti, C.; Gennari, C.; Piarulli, U. *Synlett* **2007**, 2213.