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The synthesis of S 18986, a chiral AMPA receptor modulator, via catalytic asymmetric hydrogenation

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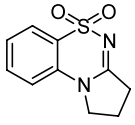
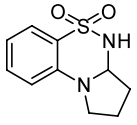
Abstract—The asymmetric hydrogenation of a dihydropyrrolo-benzothiadiazine dioxide **1** with a diphosphine ruthenium diamine catalyst has been used to synthesize the AMPA receptor positive modulator tetrahydropyrrolo-benzothiadiazine dioxide **2** (S 18986) in high enantiomeric excess. The use of factorial experimental design led to significant improvements in the process parameters and improved enantioselectivity.

Various benzothiadiazines have been shown to be potential drugs for memory and learning disorders, CNS trauma and neurodegenerative disease. In particular, racemic 2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,2,4]benzothiadiazine-5,5-dioxide **2** (Fig. 1) was shown to be a selective AMPA receptor positive modulator.[1]



Hydrogenation Substrate **1**



Racemic Thiadiazine **2**

Figure 1. Hydrogenation substrate and racemic product.

The enantiomers of racemic tetrahydropyrrolo-benzothiadiazine dioxide **2** were separated by preparative chiral HPLC and it was found that, in common with similar compounds within this therapeutic class, all activity resided in a single stereoisomer. X-Ray crystallography identified the (*S*)-enantiomer as the active component.[1] In earlier studies the enantioselective synthesis of **2** relied on the use of lithium aluminium hydride in the presence of a chiral modifier. The enantiomeric excess achieved in this reaction was reasonably high (≤76% ee), however this route presented significant disadvantages. The method required a stoichiometric amount of the chiral modifier and the reaction was incomplete, with 1–2% of the starting material present. The unreacted dihydropyrrolo-benzothiadiazine dioxide **1** had to be removed from the product before the enantiomeric purity of the enriched product could be increased via two crystallisations from acetonitrile.[1] In order to furnish a more efficient route to (*S*)-tetrahydropyrrolo-benzothiadiazine dioxide **2** (S 18986) the use of asymmetric hydrogenation of dihydropyrrolo-benzothiadiazine dioxide[2] **1** was examined.

In general, imine hydrogenation has proved to be a challenging area for metal-catalyzed asymmetric hydrogenation with only a few examples being reported where moderately high selectivity has been demonstrated.[3] The structurally related benzisothiazole dioxides have been successfully converted to their corresponding benzoisothiazoline dioxides via either catalytic asymmetric transfer hydrogenation[4] or hydrogenation.[5] Preliminary screening experiments demonstrated that none of these approaches were suitable for the asymmetric reduction of **1**. A wide range of rhodium, ruthenium and iridium catalysts were screened for both pressure and transfer hydrogenation of **1**, typically little or no reactivity was observed (<10% conversion) and the products that were obtained had very low enantiomeric excesses.

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Ruthenium precatalysts of the type [(diphosphine)$RuCl_2$(1,2-diamine)] have been shown to be extremely effective in the asymmetric hydrogenation of ketones[6] and more recently imines.[7] In excess of 40 precatalysts were screened, containing a variety of diphosphine/1,2-diamine combinations, for the asymmetric hydrogenation of **1**. In the initial screen a multiwell vessel was used, with 220 mg of substrate in 5 ml of solvent. Only biaryl ligands such as BINAP,[8] Tol-BINAP[8] and Cl-MeO-BIPHEP[9] (Fig. 2) proved to be useful for the asymmetric hydrogenation of **1**. In addition, only two 1,2-diamines gave suitable results, diphenylethylenediamine (DPEN) and diaminocyclohexane (DACH). Unexpectedly, the non-C_2 symmetric diamine DIAPEN in combination with BINAP gave a completely unreactive catalyst. For ketone reduction DIAPEN often provides the most selective and active catalyst in combination with diphosphines based on BINAP.[10]

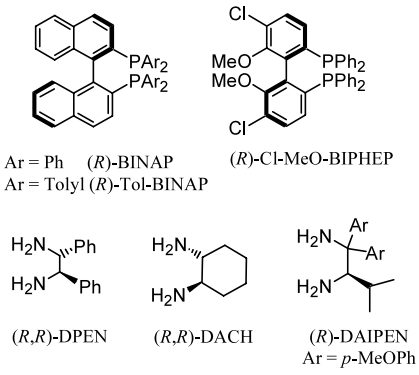


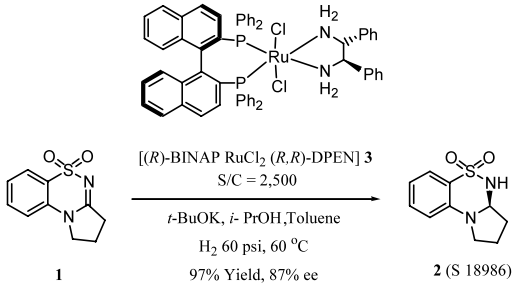
Figure 2. Selection of ligands used during initial screening.

In the initial screen high conversions (93–99%) and good enantiomeric excesses (67–75%) were obtained using catalysts based on the ligands in Figure 2. The best catalysts were examined in greater detail using single well vessels with improved stirring capability. Based on these results and the ready availability of the BINAP ligand, we chose to characterize the reaction using the [(*R*)-BINAP $RuCl_2$ (*R*,*R*)-DPEN] **3** precatalyst.

It was established that the amount of base used in the reaction was important to attaining high conversion. When utilized in the hydrogenation of ketones, precatalysts of type **3** require activation with a sub-stoichiometric amount of base (with respect to ketone). In the hydrogenation of dihydropyrrolo-benzothiadiazine dioxide **1** between 0.8 and 1.5 equiv. of base (with respect to **1**) was required to effect full conversion.

A more thorough examination of the reaction parameters were undertaken via a series of factorially designed experiments.[11] The process parameters examined were temperature, pressure and solvent composition. It was of no surprise that higher temperatures led to higher conversion, but it was interesting that hydrogen pressure had a negligible effect on conversion. The use of a mixture of toluene and isopropanol had already been identified as leading to higher enantioselectivity in preliminary experiments, although this also lead to lower solubility of the substrate and a slight reduction in conversion. Lower pressure led to slightly improved enantioselectivity as did lower temperature. Further analysis of this data identified conditions whereby complete conversion could be achieved without significant impact on the selectivity of the process. Suitable process conditions identified were 40°C, 60 psi H_2 and a 75/25 mixture of toluene/isopropanol.

Most studies up to this point had been carried out at a molar substrate to catalyst ratio (S/C) of 500. A much lower catalyst loading could be achieved (S/C = 2,500), but at the expense of reaction time. However, it had already been demonstrated that a higher temperature significantly increased the overall rate, while having only a marginally deleterious effect on selectivity. Therefore the reaction was re-examined at a higher temperature and a lower catalyst loading (higher S/C).[12] Performing the reaction at 60°C and 60 psi H_2, the product was isolated in 97% yield and 87% ee (Scheme 1). A further recrystallisation from acetonitrile provided enantiomerically pure product **2** in >99% ee.[1]



Scheme 1. Asymmetric hydrogenation of dihydropyrrolo-benzothiadiazine **1**.

We have demonstrated that the precatalyst [(*R*)-BINAP $RuCl_2$ (*R*,*R*)-DPEN] **3** can be used for the asymmetric hydrogenation of a novel *N*-sulfonylimine substrate, the dihydropyrolo-benzothiadiazine dioxide **1**. This could provide an efficient process for the manufacture of the chiral AMPA receptor positive modulator **2** (S 18986). Further applications of [(diphosphine) $RuCl_2$ (1,2-diamine)] precatalysts are being investigated and will be reported in due course.

Acknowledgements

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11. MODDE 5.0, Umetrics AB (www.umetrics.com).
12. A pressure vessel was charged with 2,3-dihydro-1*H*-pyrrolo[2,1-*c*][1,2,4]benzothiadiazine-5,5-dioxide **1** (100 g, 450 mmol) and toluene (750 ml). A nitrogen atmosphere was established. A solution of potassium butoxide (56.3 g, 502 mmol) in propan-2-ol (250 ml) was added followed by [(*R*)-BINAP $RuCl_2$ (*R*,*R*)-DPEN] (186 mg, 0.185 mmol). The mixture was heated to 60°C and the vessel was charged with 60 psi hydrogen. The reaction mixture was stirred for 6.5 h, maintaining the hydrogen pressure between 50–65 psi. Once cooled and acidified, the product was collected by filtration and dried to give 98 g (97% yield) of (*S*)-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*]-[1,2,4]benzothiadiazine-5,5-dioxide **2**. HPLC analysis showed 99.4% chemical purity 87% ee. Chiral HPLC: Daicel Chiralpak AS column, UV 212 nm, 1.0 ml/min, 30% heptane, 70% ethanol for 10 min, ramp to 100% ethanol in 1 min, hold for 12 min. Retention time (*R*)= 5.0 min, (*S*)=10.6 min. Two recrystallisations from acetonitrile[1] afforded **2** in >99% ee.