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Diastereoselective hydrogenation of folic acid esters with the Daniphos ligand

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Abstract

Folic acid dimethylester benzenesulfonate was hydrogenated homogeneously in a rhodium-catalyzed diastereoselective reaction employing a set of the previously published planar-chiral "Daniphos" ligands, which are based on an arene chromium tricarbonyl scaffold. Diastereoselectivities of up to 42% *de* were achieved, almost matching the benchmark ligand BINAP. An X-ray structure of the most successful ligand P(*i*-Pr_2)/PPh_2 is presented and discussed.

Keywords: Rhodium; Diphosphines; Planar chirality; Asymmetric hydrogenation

1. Introduction

Asymmetric catalysis is undoubtfully the most powerful method for the synthesis of optically active compounds as it is possible to gain a maximum amount of enantiomerically enriched product at the expense of only catalytic amounts of a chiral catalyst which normally consists of a transition metal and an enantiomerically pure ligand. The nobel-prize winners Knowles, Noyori and Sharpless [1] layed the foundation of a modern transition-metal catalysis used on an industrial scale for the production of fine chemicals [2c], fragrances, agrochemicals and pharmaceutical intermediates (API, active pharmaceutical ingredients). Besides the well-known cases of the *Takasago*-process for the production of (−)-menthol [1b,1d] and the *Syngenta* herbicide (*S*)-Metolachlor [2a,2b], which involves an asymmetric hydrogenation employing the JOSIPHOS-ligand, more recent examples are *AstraZeneca*'s heartburn drug Esomeprazole by an asymmetric oxidation [3], *Novartis*' antihypertensive drug Valsartan [4] and *BASF*'s fungicide Boscalid (Nicobifen) [5] by *Suzuki*-coupling and the production of Ibuprofene by Pd-catalyzed carbonylation and the fragrance Civetone by Ru-catalyzed metathesis by *BASF* [5]. L-Tetrahydrofolic acid is a versatile intermediate for the manufacturing of different folates e.g., L-leucovorin [7], which is used in cancer therapy or Metafolin which is used as a vitamin in functional food. To our knowledge optically pure L-tetrahydrofolic acid is still obtained by repeated fractional crystallisation from an equimolar mixture of diastereoisomers formed by non-diastereoselective hydrogenation of folic acid. In order to increase the yield of L-tetrahydrofolic acid and to avoid recrystallisation steps, we checked the utility of our recently developed planar-chiral ligand, "Daniphos" [6] for the diastereoselective hydrogenation of folic acid dimethylester-benzenesulfonate. A sketch of the Daniphos ligand is given in Fig. 1.

2. Results and discussion

The hydrogenation of folic acid dimethyl ester benzenesulfonate is presented in Fig. 2. In this reaction the diazadiene system of the pteridine ring of the substrate is hydrogenated, giving a new stereogenic center at position

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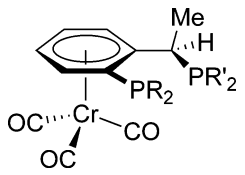

Fig. 1. The "Daniphos"-ligand.

6. The distance of the stereogenic center of the glutamic acid residue is too far from the newly formed chiral center and therefore it does not cause any measurable stereochemical induction in the hydrogenation and the outcome of the reaction is governed by the chiral ligand alone. Quite a number of experiments have been undertaken so far to reach a reasonable induction, but the best results achieved do not exceed some 40% *de*, in which the desired product is the (*S*,*S*)-diastereomer [8]. In the course of the reaction, a significant percentage of an undesired cleavage product is observed in varying amounts ($ABGAMe_2$, aminobenzoylgluamic acid dimethylester), depending on the ligand used, diminishing the yield of the valuable tetrahydrofolic acid dimethylester ($THFMe_2$).

A number of candidates from our ligand library has been employed in this survey, bearing aliphatic as well as aromatic substituents on the phosphorus donor atoms. They are summarized in Fig. 3, together with the benchmark ligands Josiphos and BINAP, which also were included in this examination for reasons of comparison (all ligands are configured (*R*) with respect to central as well as planar chirality except for ligand **1**, where also the (*S*,*S*)-enantiomer was employed). The results are collected in Table 1.

From the results achieved with ligand **1**, it can be seen that the use of the other enantiomer of the ligand results in a reversal of the configuration in the product together with (nearly) the same induction, as is to be expected. Moreover, it is remarkable that all derivatives that carry only aromatic substituents on the phosphorus donor atoms deliver preferably the undesired (6*R*,*S*) diastereomer. In contrast to this, the desired isomer is formed in excess when the ligands contain aliphatic side chains on the donor centers as well (it should be kept in mind that all ligands are configured (*R*,*R*)). Here, an especially high stereochemical induction and chemical yield of tetrahydrofolic acid ester is achieved in case of the P(*i*-Pr)$_2$/PPh$_2$ derivative **2**. So one might conclude that a sterically demanding, Lewis-basic group in the *ortho*-position influences the reaction in the desired direction. In case of the purely aromatic candidates the differences in optical yields are less pronounced: they range between 20% and 30% *de*. Better values are

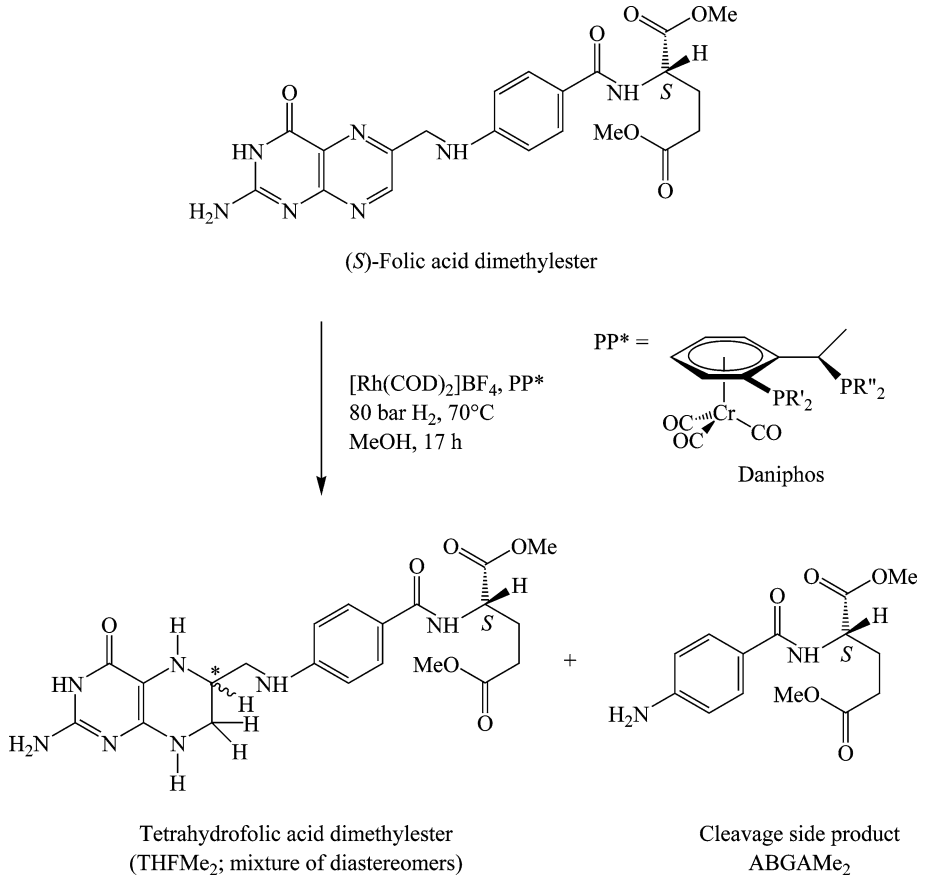

Fig. 2. Hydrogenation of folic acid dimethylester.