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Synthesis and applications of diphosphine ligands derived from the lignan hydroxymatairesinol

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ABSTRACT

Highly efficient methods for synthetic modifications of the natural lignan hydroxymatairesinol into chiral diphosphines similar to DIOP were developed. Catalytic activity and induction of enantioselectivity for the prepared phosphines were evaluated in rhodium catalyzed hydrogenations of different functionalized alkenes. High catalytic activities were observed with low catalyst loading at atmospheric pressure. The phosphines showed moderate to high enantioselectivity depending on the substrate used. Hydrogenation of 1-acetamidostyrene gave 84% *ee* of the *S*-enantiomer.

1. Introduction

The increasing demand to produce enantiomerically pure pharmaceuticals, agrochemicals, flavors, and other fine chemicals requires the development of new, more effective and cheaper methods of asymmetric catalysis. Utilization of natural chiral molecules as ligands in asymmetric catalysis is one way to increase the efficiency. Recent development in the field of biorefinery has made several wood-based natural products available in large-scale. The isolation and purification of lignans from knotwood of coniferous species has received much attention. For example, separation of hydroxymatairesinol from knotwood of Norway spruce has made it possible to study this lignan more in detail. Hydroxymatairesinol has been shown to have interesting biological activity such as anticancer and antioxidant activity and new application areas for its utilization are of great interest. Here we report the transformation of hydroxymatairesinol to chiral diphosphines for applications in chiral catalysis.

One of the most important reactions in this field of catalysis is the transition metal catalyzed asymmetric hydrogenation. This reaction requires a chiral ligand to create the asymmetric environment and to stabilize the metal complex. Phosphine ligand has been proven to be the most suitable for this purpose.

(4*R*,5*R*)-4,5-Bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane (DIOP) was one of the first chiral ligands used for asymmetric catalysis [1]. However, DIOP itself provided only moderate to good enantioselectivities in asymmetric hydrogenations of dehydroamino acid derivatives. Tang at al. [2] proposed as a possible reason that the seven-membered chelate ring of the DIOP metal complex is conformationally flexible. Indeed introduction of the substituent into -CH_2-P arm significantly improves the selectivity (DIOP*) [3]. On the other hand, similar diphosphines with more rigid 6-membered ring in their backbone like sk-Phos, provides excellent selectivity in a number of reactions [4]. Nevertheless, only a few chirally pure diphosphines similar to DIOP, not derived from tartaric acid, has been described in literature [5–7].

We recently reported that the readily available lignan hydroxymatairesinol from knotwood of Norway Spruce can be transformed to chiral 1,4-diols [8,9]. Here we present the concept of using hydroxymatairesinol for preparation of different (similar to DIOP) diphosphine ligands and their application in asymmetric hydrogenations. The use of hydroxymatairesinol as a starting material, gives an access to the enantiopure butyrolactone with the 8R,8′R configuration similar to DIOP (Fig. 1). The structure of hydroxymatairesinol allows modifications of the phenolic functions, electron rich aromatic rings, the benzylic alcohol group and the

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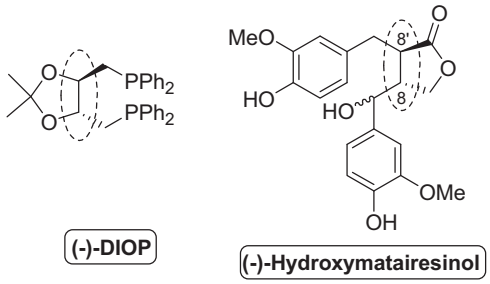

Fig. 1. Similarity in stereochemistry for DIOP and hydroxymatairesinol.

butyrolactone ring which provides a number of possible derivatives and backbones.

2. Experimental

2.1. General methods

Unless otherwise stated, chemicals were obtained from commercial suppliers and used without further purification. A knotwood extract containing hydroxymatairesinol was supplied by UPM Ltd. THF and toluene were dried by the sodium-benzophenone method immediately prior to use. DMF and DCM were dried by distilling from CaH_2. NMR spectra were recorded with Bruker Avance 600 MHz NMR spectrometer using standard pulse sequences. Chiral HPLC analyses were performed with a HPLC chromatograph equipped with a Daicel HPLC column Chiralcel OD-H. Chiral GC analyses were performed with a gas chromatograph equipped with a Varian capillary column CP-Chirasil-Dex CB. HRMS were recorded using a Bruker Micro Q-TOF instrument with ESI (electorspray ionization) operated in positive mode. The reactions were monitored by TLC. Aluminum based TLC plates (Merck) silicagel 60 F_{254} were used.

Analytical data for the prepared compounds (NMR, HRMS, elemental analyses) and for asymmetric reactions (chiral LC and GC chromatograms) are presented in Supporting Information (SI).

2.2. General method for preparation of diols (*5*, *6*, *7*, *8*) (Scheme 2)

Lactone (**1**, **2**, **3** or **4**) (5 mmol) was dissolved in tetrahydrofuran (30 ml) and the solution was cooled down to 0 °C. Lithium aluminum hydride (2.5 ml of 4 M solution in Et_2O, 10 mmol) was added dropwise over a period of 0.5 h. The reaction mixture was stirred for 2 h at room temperature. Then 1 ml of 10% NaOH in water was added carefully drop by drop and the suspension was filtered and the precipitate was washed with hot THF. The filtrates were combined and the solvent was evaporated to give the final product (**5**, **6**, **7** or **8**) as a white powder.

Starting material (lactone)	Product (diol)	Yield, %
1	**5**	88
2	**6**	87
3	**7**	75
4	**8**	74

2.3. General method for preparation of dimesylates (*9*, *10*, *11*, *12*) (Scheme 3)

Diol (**5**, **6**, **7** or **8**) (1 mmol) was dissolved in DCM (20 ml) and TEA (0.35 ml, 2.5 mmol) was added followed by addition of mesyl chloride (0.17 ml, 2.2 mmol). The mixture was stirred at room temperature for 16 h and then it was washed with water (2 × 30 ml), dried over sodium sulfate and concentrated to dryness. The residue was purified by flash chromatography in chloroform to give product as a colorless solid.

Starting material (diol)	Product (dimesylate)	Yield, %
5	**9**	96
6	**10**	62
7	**11**	95
8	**12**	97

2.4. Sodium diphenylphosphide

To a solution of diphenylphosphine (50 mmol, 8.7 ml) in dry THF (30 ml) sodium metal (52 mmol, 1.2 g) was added as small pieces over 1.5 h. The mixture was stirred for 6 h until all sodium was dissolved and the solution of the sodium diphenylphosphide was diluted with dry THF to 50 ml.

2.5. General method for preparation of the phosphines (*13*, *14*, *15*, *16*) (Scheme 3)

Dimesylate (**9**, **10**, **11** or **12**) (0.5 mmol) was dissolved in THF (30 ml) and 1 M THF solution of the sodium diphenylphosphide (1.5 ml, 1.5 mmol) was added dropwize. The mixture was stirred for 18 h at room temperature and then it was concentrated to dryness. The residue was purified by flash chromatography to give the target diphosphine as a colorless solid.

Starting material (dimesylate)	Product (diphosphine)	Yield, %
9	**13**	90
10	**14**	87
11	**15**	91
12	**16**	88

2.6. General method for asymmetric hydrogenation reaction

2.6.1. Preparation of the stock solution of the catalyst

Dichloro-tetraethylene-dirhodium (14 mg, 0.035 mmol) was dissolved in THF (2 ml) and phosphine (**13**, **14**, **15** or **16**) (0.074 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 12 h. The prepared solution of the catalyst had a concentration of 0.035 M.

2.6.2. Catalytic reaction

Substrate **18** (0.7 mmol, 154 mg) or **20** (0.7 mmol, 114 mg) was dissolved in methanol (2 ml) and stock solution of the catalyst was added (0.1 ml, 0.5 mol %, or 0.2 ml, 1 mol %). Hydrogen was bubbled through the solution for 1 h. The reaction mixture was analyzed by GCMS and by chiral GC. All conversions were over 95%. The selectivities of the reactions are presented in Tables 1 and 2.

3. Results and discussion

To prepare a diverse scope of lignan-derived phosphines, hydroxymatairesinol was transformed into four different lactones by methods described in our previous publications (Scheme 1) [8,9]. In short, dimethylmatairesinol (**1**) was prepared from hydroxymatairesinol by hydrogenolysis on palladium to matairesinol [10] followed by methylation of the phenolic hydroxyls. Dimethylconidendrin (**2**) was obtained by methylation of the phenolic hydroxyls of the lignan conidendrin, which forms quantitatively in acidic conditions from hydroxymatairesinol [11]. Lactone **3** was prepared from **1** by intramolecular oxidative coupling mediated by vanadium oxyfluoride. For preparation of the macrocyclic compound **4**, the phenolic groups of matairesinol were first allylated and then cyclized by ring-closing metathesis, followed by hydrogenation of the double bond [9].