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Synthesis of new chiral diphosphine ligand (BisbenzodioxanPhos) and its application in asymmetric catalytic hydrogenation

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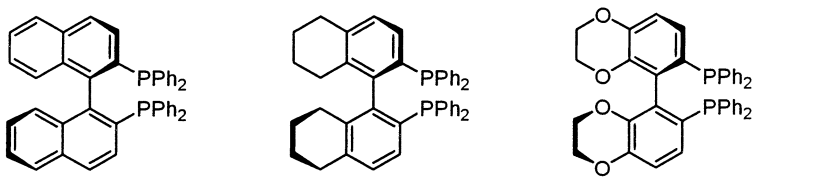
Abstract—The new chiral diphosphine ligand [(5,6), (5′,6′)-bis(1,2-ethylenedioxy)biphenyl-2,2′-diyl]bis(diphenylphosphine) (BisbenzodioxanPhos) has been successfully prepared and used in ruthenium-catalyzed asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid and β-keto esters with high enantioselectivity (92.2% and up to 99.5% ee, respectively). © 2002 Published by Elsevier Science Ltd.

Atropisomeric C_2-symmetric phosphine ligands have played crucial roles in the development of asymmetric catalysis.[1] Although many chiral diphosphine ligands have been prepared and applied in asymmetric catalytic hydrogenation reactions, and excellent results have been achieved in a number of reactions,[2] the design and development of new chiral diphosphine ligands for transition metal complex-catalyzed commercially attractive reactions is still an area of high interest.

Among the chiral ligands studied, atropisomeric diphosphines of the BINAP type have found widest application in transition metal-catalyzed reactions due to their spectacular asymmetry-inducing capability.[2] The BINAP family of ligands are outstanding in the asymmetric hydrogenation of 2-arylacrylic acids in which most other chiral ligands are ineffective. Chiral diphosphine ligands of the type H_8-BINAP have been shown to be superior to their binaphthyl counterparts in a series of asymmetric catalytic reactions.[3–6] Our previous studies have shown that chiral ligands bearing the H_8-BINOL structure induced higher enantioselectivity in a series of asymmetric reactions as compared to BINOL, due possibly to the more bulky structure of H_8-BINOL.[7–10] To expand further the scope of these findings, it is of high interest to design chiral ligands similar to H_8-BINAP but with added functionalities (Fig. 1).

Hetero-aromatic compounds have provided a variety of opportunities for the synthesis of chiral phosphine ligands for asymmetric catalytic reactions, and many new chiral hetero-aromatic biarylphosphines such as tetraMe-bitianp,[11] bitianp,[12] bimip,[13] biscap,[13] BIBFUP,[14,15] SEG-PHOS,[16] and BIFAPS[17] have recently been reported. In this communication we report the



R-BINAP *R*-H_8-BINAP *R*-BisbenzodioxanPhos

Figure 1.

Keywords: BisbenzodioxanPhos; hydrogenation; β-keto esters; naproxen.

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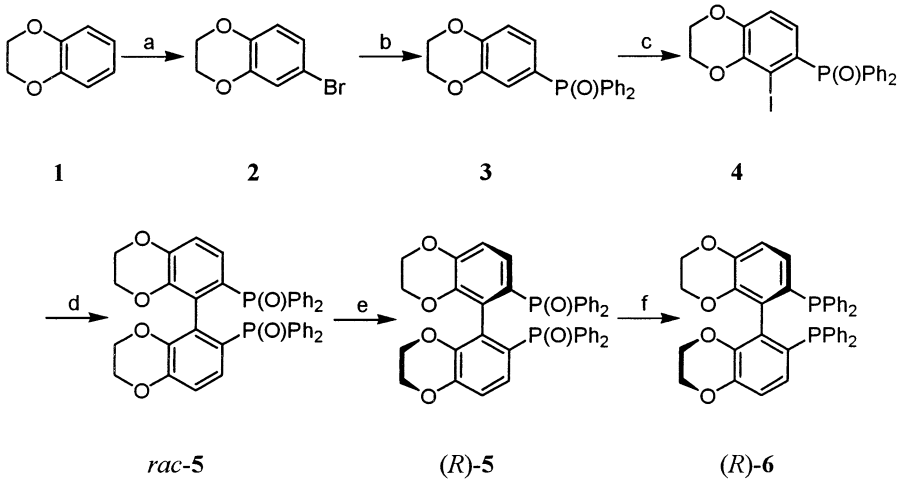
synthesis of a new type of chiral ligand ([(5,6),(5′,6′)-bis(1,2 - ethylenedioxy)biphenyl - 2,2′ - diyl]bis(diphenylphosphine) (BisbenzodioxanPhos, **6**)) and the application of its ruthenium complexes in two classes of asymmetric catalytic hydrogenation reactions which are of commercial interest.

BisbenzodioxanPhos bears a bis-benzodioxane structure, a structural feature similar to that of H_8-BINAP. It is expected to show good reactivity and selectivity in asymmetric catalytic reactions in which BINAP is uniquely useful. The dioxane part of the backbone also offers good opportunities for easy modification and tuning. The synthetic route to compound **6** is outlined in Scheme 1.[18]

Compound **1** is commercially available and can be readily brominated according to a known procedure[19] to provide compound **2** in almost quantitative yield. Lithiation of **2** with *n*-butyl lithium in THF at −78°C, followed by the addition of chlorodiphenylphosphine and subsequent oxidation with hydrogen peroxide produced phosphine oxide **3**. A sequence of *ortho*-lithiation/iodination[20] with LDA via a thermodynamically controlled process instead of the generally used iodination with diiodoethane gave product **4** in 75% isolated



Scheme 1. The synthetic route to (*R*)-BisbenzodioxanPhos. (a) Br_2, HOAc, rt, 100%; (b) (1) *n*-BuLi, THF, −78°C (2) $ClPPh_2$, −78°C to rt (3) H_2O_2, 0°C, acetone, 93%; (c) (1) LDA, THF, −78°C (2) 1,2-diiodoethane, −78°C to rt, 75%; (d) Cu, DMF, 140°C, 85%; (e) (1) resolution, (−)-DBTA, CH_2Cl_2:EA:EtOH = 1:2:1.7, 7 days (2) NaOH, 44%; (f) $HSiCl_3$, toluene, 140°C, 83%.

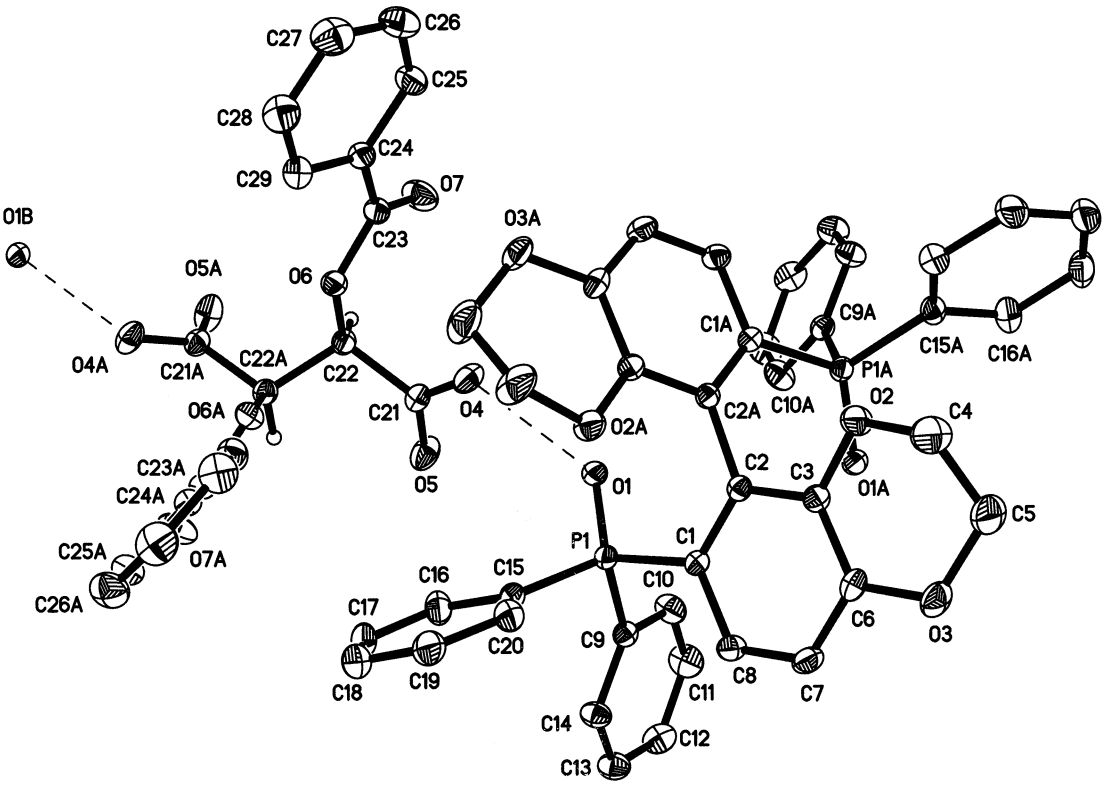


Figure 2. The ORTEP drawing of (−)-DBTA·(*R*)-**5**.

yield. The racemic bis(diphenylphosphine oxide) **5** was obtained in good yield (85.2%) via Ullmann coupling[21] of the iodophosphine oxide **4**. The enantiomers of **5** can be resolved using either (−)-2,3-dibenzoyl tartaric acid or (+)-2,3-dibenzoyl tartaric acid [(−)- or (+)-DBTA] as the resolving agent. (*R*)-Phosphine oxide was obtained when (−)-DBTA was used as the resolving agent. The structure and the absolute configuration of the complex was determined by single-crystal X-ray diffraction of (−)-DBTA·(*R*)-**5** (Fig. 2).

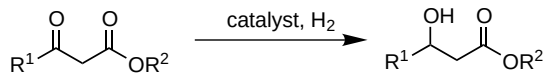
The enantiomeric purity of **5** was determined by HPLC using a chiral column (Daicel AD). The chiral ligand BisbenzodioxanPhos (**6**) was obtained with enantiomeric purity of over 99.9% upon the reduction of its phosphine oxide precursor **5** with trichlorosilane at 140°C.

Whether the dioxane units of the ligand may provide enough steric hindrance to preserve the configuration of **6** and whether racemization may occur during the high temperature reduction process are interesting questions. To test if racemization occurred during the high temperature reduction process and to measure the enantiomeric purity of the ligand, the resolved enantiomerically pure diphosphine **6** was oxidized back to its diphenylphosphine oxide using H_2O_2 and the enantiomeric composition of the oxidized product was measured. The experimental result clearly showed that racemization did not occur during the trichlorosilane reduction step.

Ru[(*R*-**6**)Cl_2(DMF)$_n$] (**7**) and Ru[(*R*-**6**)Cl(*p*-cymene)]Cl (**8**) were prepared by using procedures reported by Windscheif et al. and Mashima et al.,[22,23] and the complexes were characterized by ^{1}H and ^{31}P NMR spectra. These complexes were used as catalysts for the subsequent hydrogenation study without further purification.

The experiments on the hydrogenation of β-keto esters were carried out in a Parr stainless steel high pressure reactor under 50 psi H_2 pressure at 80–90°C. The results shown in Table 1 revealed that the new catalyst was highly enantioselective in this class of reactions.[24]

Table 1. The asymmetric hydrogenation of β-keto esters with **7**



Entry[a]	R^1	R^2	Conv. (%)	ee (%)
1[b]	CH_3	CH_3	100	98.1
2[b]	CH_3	Et	100	99.5
3[c]	CH_3	Bn	100	96.9
4[b]	$ClCH_2$	Et	100	97.0

[a] The hydrogenation was carried out in 50 ml autoclave; 50 psi of H_2; solvent 2.5 ml (methanol or ethanol); 100 mg of substrate (0.38–0.2 M); 0.5 mg of catalyst **7** (ca. 0.2 mM); the reaction time was 12–24 h; the reaction temperature was 80–90°C; the configuration of product was *R*.

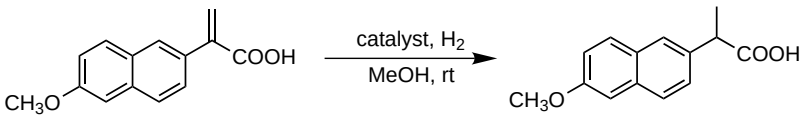
[b] Enantiomeric excess was determined by GC analysis (CHROMPACK WCOT fused silica 25 M×0.25 MM coating CP CHIRASIL-DEX CB) after converting the product to the corresponding acetate derivative.

[c] Enantiomeric excess was determined by GC analysis (CHIRALDEX G-PN) after converting the hydrogenation product to the corresponding acetate derivative.

The asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid was also studied using **8** as the catalyst. The naproxen product, a nonsteroidal drug with anti-inflammatory, analgesic and antipyretic activity,[25–27] was obtained in high ee. The enantiomeric excess of naproxen obtained using **6** as chiral ligand compared favorably with that using BINAP as the chiral ligand under similar reaction conditions (1000 psi H_2 pressure and ambient temperature, entry 2 in Table 2).[6,12,23,25,28] It should be noted that this commercially attractive reaction has been extensively studied in the past two decades and except for the BINAP type of ligands, most other ligands proved ineffective. The development of new catalysts with improved enantioselectivity is therefore highly desirable.

The effect of hydrogen pressure on the enantioselectivity of the reaction is shown in entries 1–4 of Table 2. Higher hydrogen pressure gave better enantiomeric excess in the product.

Table 2. The asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid with **8**



Entry[a]	H_2 pressure (psi)	Conversion (%)	ee[b] (%)
1	1700	100	92.2
2	1000	100	91.0 (89.0)[c]
3	500	100	89.2
4	100	100	67.4

[a] Reactions carried out in a 50 ml autoclave; 2.5 ml of methanol as solvent; 5 mg of substrate (8.8 mM); 0.25 mg of catalyst **8** (0.1 mM based on Ru); ambient reaction temperature (20–25°C).

[b] The enantiomeric excess was determined by HPLC analysis with a SUMICHIRAL OA-2500 column.

[c] This reaction was carried out using (*S*)-BINAP as the ligand under the same reaction conditions.

In conclusion, we have designed and prepared an effective chiral atropisomeric ligand BisbenzodioxanPhos using a convenient synthetic route. This ligand forms well-defined ruthenium complexes which offer high enantioselectivities in the catalytic hydrogenation of a variety of β-keto esters and 2-(6′-methoxy-2′-naphthyl)propenoic acid. The application of this new ligand in other asymmetric catalytic reactions is being studied.

Acknowledgements

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