# A New Modular Class of Easily Accessible, Inexpensive, and Efficient Chiral Diphosphine Ligands for Homogeneous Stereoselective Catalysis

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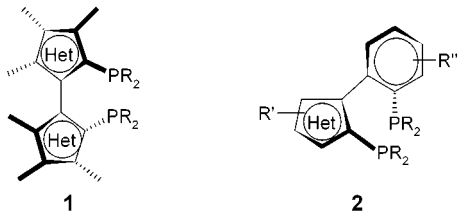
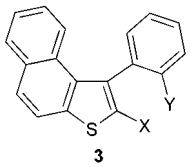
The search for new chiral ligands capable of high enantioselectivity in homogeneous catalysis is a current challenge in applied chemical research. Chelating diphosphines supported on stereogenic atropisomeric biaryl scaffolds are rated as very efficient chiral modifiers in most stereoselective reactions.[1] The electron density at the donor centers of these ligands is a crucial parameter controlling both reaction kinetics and stereoselectivity.[2] We demonstrated that an accurate tuning can be effected by exploiting the inherently differentiated electron-demand or electron-releasing ability of five-membered aromatic heterocyclic systems in $C_2$-symmetric diphosphino biheteroaryls **1**,[3] which possess high stereoselection ability and are, in general, synthetically more accessible than carbocyclic biaromatic systems[4] (Chart 1). The nature of the heterocyclic system constituting the backbone and the position of the diphenylphosphino groups on it strongly influence the electronic properties at phosphorus, which ranges gradually from very electron poor to very electron rich situations.[3] It is known, however, that the homotopism of the chelating centers is not a prerequisite for high enantioselectivity, and constitutionally and electronically diverse phosphorus characterize $C_1$ symmetry controllers of high efficiency.[5] We considered that the electronic modularity offered by the five-membered heteroaromatic systems could be combined with a very easy synthesis in the $C_1$ symmetry

**Chart 1**




**1** **2**

**Chart 2**




**3**

**a**: X = Y = $PPh_2$
**b**: X = Y = $POPh_2$
**c**: X = H; Y = Br
**d**: X = $PPh_2$; Y = H

diphosphines **2**, having atropisomeric five-membered heterocyclic-six-membered carbocyclic biaromatic backbones (Chart 1).

In these cases, the synthetic approach is merely reduced to the preparation of aryl-substituted five-membered heterocycles. The most relevant point of this design is the possibility to gain entry into an unlimited, highly modular class of ligands. The electronic density on the phosphine group on the heterocyclic ring could be tuned through the same strategy applied for diphosphino biheteroaryls **1**, while that of the phosphine group on the carbocyclic moiety through tailored substitution on it.

We report here the synthesis of enantiopure diphosphine **3a** as the prototype of this new class of asymmetric ligands, and the preliminary data of the application of their ruthenium, rhodium, and palladium complexes as homogeneous catalysts in some homogeneous catalysis experiments (Chart 2).

Structural design for **3a** was based on the assumption that it was desirable to substantially differentiate the electronic properties of the phosphine groups, to direct the approach of the substrate to the heterotopic bonding sites of the catalytic complex along a single, energetically preferred, path. The use of inexpensive, commercially available starting materials was also considered as a project prerequisite.

Polyphosphoric acid (PPA)-promoted cyclodehydration (62% yields) of 1-(2-bromophenyl)-2-(2-naphthylthio)-ethanone (**4**), prepared by condensation (90% yields) of sodium $\beta$-naphthalenethiolate with $\omega$,2-dibromoacetophenone, afforded 3-(2-bromophenyl)naphtho[2,1-*b*]thiophene (**3c**). Simultaneous transmetalation of the aryl bromide and acid−base lithiation of the thiophene ring, effected with butyllithium, quenching of the dianion with 2 equiv of chlorodiphenylphosphine, followed by in situ hydrogen peroxide treatment, gave phosphine oxide (±)-**3b** (53% yields) (Scheme 1).

The racemate was resolved by fractional crystallization of the diastereomeric adducts obtained by reaction with (+)- and (−)-dibenzoyltartaric acids. Alkaline decomplex-

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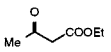
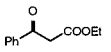
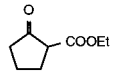
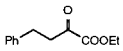
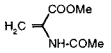
**Table 1. Hydrogenation of Functionalized C=O and C=C Bonds Using Ligand 3a**

| Cat. | Substrate | S/C | $P_{H_2}$ [Kg/cm$^2$] | T [°C] | t [h] | ee [%] | Product Conf. |
|---|---|---|---|---|---|---|---|
| **5a** |  | 1000 | 100 | 40 | 3.5 | 96 | R |
| **5a** |  | 240 | 100 | 55 | 6 | 73 | S |
| **5a** |  | 1000 | 100 | 40 | 8 | 97 (de=74%) | 1S,2S |
| **5b** |  | 243 | 100 | 50 | 24 | 85 | S |
| **5b** |  | 445 | 100 | 50 | 30 | 93 | S |
| **5c** |  | 1000 | 3.7 | 25 | 60 | 74 | S |

**Scheme 1**

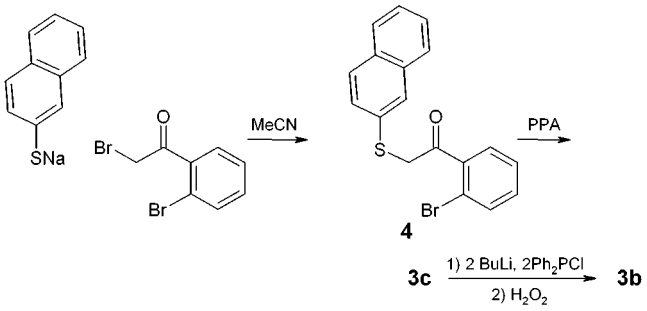
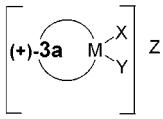


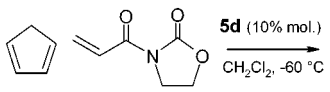

**Chart 3**

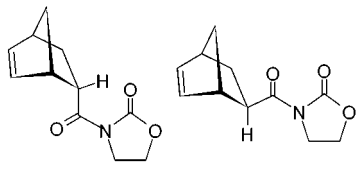



**5**

**a**: M = Ru X = Y = Cl
**b**: M = Ru X = $C_6H_6$ Y = Z = Cl
**c**: M = Rh X, Y = cod Z = Cl
**d**: M = Pd X, Y = $ClO_4$

**Scheme 2**



endo 95% ee% = 75 exo 5%

ation of the adducts afforded enantiopure phosphine oxides (+)-**3b** and (−)-**3b**, which were reduced to the corresponding enantiopure diphosphines (+)-**3a** and (−)-**3a** with trichlorosilane.

The electrochemical oxidative potential ($E°$ , V) was chosen as parameter for evaluating the electronic availability of the phosphine groups of **3a**. Voltammetric experiments showed a single irreversible oxidation peak at 0.74 V, attributable to the diphenylphosphine group located on the phenyl ring. The electrochemical oxidative potential of the phosphine group on the thiophene moiety was inferred from the $E°$ value (0.91 V) found for the 3-phenyl-2-(diphenylphosphino)naphtho[2,1-*b*]thiophene **3d**, prepared by reaction of the lithium anion of known 3-phenylnaphtho[2,1-*b*]thiophene[6] with chlorodiphenylphosphine. These values confirm that the two phosphorus atoms of **3a** possess very different electronic properties: the former is a rather electron-rich phosphine group, while the latter is a quite electron-poor function.

The preliminary catalysis experiments with **3a** were performed in the hydrogenation of substrates that are in standard use for the evaluation of the catalytic properties of all new chiral ligands appearing in the literature (Table 1) and in the Diels−Alder cycloaddition of cyclopentadyene and *N*-acryloyloxazolidin-2-one (Scheme 2).

$Ru^{II}$ complexes **5a**,**b** (Chart 3) were applied in the reduction of the ketonic function of α- and *β*-oxoesters. $Rh^{I}$ complex **5c** was employed in the hydrogenation of methyl 2-acetamidoacrylate to methyl *N*-acetylalaninate and $Pd^{II}$ perchlorate complex **5d** in Diels−Alder cycloaddition.

The enantioselection data obtained in these experiments are illustrated in Table 1 and in Scheme 2.

These data, though resulting from unrefined experiments, demonstrate that diphosphine **3a** possesses a quite good stereoselection capacity. Even though the enantioselection levels found in the hydrogenation of 2-acetamidoacrylate and in the Diels−Alder cycloaddition are definitely lower than those achievable with chiral ligands specifically designed for these reactions, the enantiomeric excesses obtained in *β*-ketoesters and methyl phenylglyoxylate hydrogenation are fully comparable to those produced by the most efficient ligands. When considering that a preliminary cost estimate for enantiopure **3a** is less than one tenth of DuPHOS, one-fifth of BINAP and one-third of tetraMe-BITIOP,[4b] it appears that the class of the $C_1$ symmetry diphosphines **2** may

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offer a countless multitude of new highly modular and efficient chiral modifiers for industrial homogeneous catalysis.

## Experimental Section

**1-(2-Bromophenyl)-2-(2-naphthylthio)ethanone (4).** Dry sodium 2-naphthalenethiolate [from naphthalenethiol (10.0 g) and NaOMe] was rapidly added to a stirred solution of *ω*,2-dibromoacetophenone[7] (17.3 g) in MeCN (200 mL) at 5 °C. Standard workup gave **4** as a viscous oil (20.6 g) that was used in a crude state. $^1$H NMR ($CDCl_3$): $\delta$ 4.37 (s, 2H, $CH_2$), 7.20−7.32 (m, 3H), 7.40−7.60 (m, 4H, $C_6H_4$), 7.69−7.80 (m, 4H).

**3-(2-Bromophenyl)naphtho[2,1-*b*]thiophene (3c).** A mixture of compound **4** (20.0 g) and PPA (200 g) was heated under stirring at 100 °C for 1 h, poured onto ice, neutralized with a 20% $NH_4OH$ solution, and extracted with $CH_2Cl_2$. The organic layer was dried and filtered on a silica gel cake to give **3c** (11.8 g). Mp: 99 °C (hexane). $^1$H NMR ($CDCl_3$): $\delta$ 7.25 (t, 1H), 7.38 (s, 1H), 7.35−7.55 (m, 5H), 7.78 (d, 2H), 7.94 (d, 2H).

**(±)-3-[2-(Diphenylphosphinyl)phenyl]-2-(diphenylphosphinyl)naphtho[2,1-*b*]thiophene [(±)-(3b)].** BuLi (2.5 M in hexane, 20.6 mL) was dropped into a solution of **3c** (8.0 g) and TMEDA (8 mL) in THF (200 mL) at −70 °C. After 1 h at rt, $Ph_2PCl$ (8.8 mL) was added, the solvent removed, and the residue treated with $CH_2Cl_2$ (200 mL) and a 15% $H_2O_2$ solution (60 mL). Standard workup gave **3b** (8.3 g). Mp: 303 °C (AcOEt). MS: *m*/*z* 660 ($M^+$); 583 ($M^+ - C_6H_5$); 459 ($M^+ - PO(C_6H_5)_2$). $^1$H NMR ($CDCl_3$): $\delta$ 6.83−7.04 (m, 4 H), 7.04−7.20 (m, 4 H), 7.20−7.90 (m, 22 H); $^{31}$P NMR ($CDCl_3$): $\delta$ 20.5 (s, 1 P), 28.1 (s, 1 P).

**Resolution of (±)-3b.** Crystallization from AcOEt/$CHCl_3$ 1:1 of the diastereomeric adducts formed by reaction of (±)-**3b** with an equimolar amount of (+)-*O*,*O*′-dibenzoyl-D-tartaric acid gave the dextrorotatory diastereoisomer as the less soluble adduct (mp 268 °C; $[\alpha]^{25}_D$ = +63.6, *c* = 0.42 in EtOH). Alkaline treatment gave enantiopure (+)-**3b** (mp 268 °C (synt. 125 °C); $[\alpha]^{25}_D = -310$, *c* = 0.38 in $C_6H_6$). The mother liquors were treated with a 0.75 M NaOH solution and the resulting diphosphine oxide, treated in turn with (−)-*O*,*O*′-dibenzoyl-L-tartaric acid, gave the levorotatory adduct ($[\alpha]^{25}_D = -63.6$, *c* = 0.42 in EtOH). Alkaline treatment gave enantiopure (−)-**3b** (mp 267 °C (sint. 125 °C); $[\alpha]^{25}_D = +305.5$, *c* = 0.37 in $C_6H_6$). Enantiomeric purity of (+)- and (−)-**3b** was checked by HPLC (Chiracel OD, Daicel Chem Ind.; hexane/*i*-PrOH 99.8:0.2).

**(+)- and (−)-3-[2-(Diphenylphosphino)phenyl]-2-(diphenylphosphino)naphtho[2,1-*b*]thiophene [(+)-(3a)] and (−)-3a].** Reduction of phosphine oxides to phosphines was effected according to known methodologies.[4b] Enantiopure (+)-**3b** gave enantiopure (−)-**3a** (mp 325 °C dec; $[\alpha]^{25}_D = -185$, *c* = 0.39 in $C_6H_6$), while enantiopure (−)-**3b** gave enantiopure (+)-(**3a**) (mp 325 °C dec; $[\alpha]^{25}_D = +172$, *c* = 0.38 in $C_6H_6$). Enantiomeric purity of (+)-**3a** and (−)-**3a** was checked after reoxidation to phosphine-oxides. MS: *m*/*z* 443 ($M^+ - P(C_6H_5)_2$). $^1$H NMR ($CDCl_3$): $\delta$ 6.82 (t, 2 H), 6.87 (t, 2 H), 7.0 (t, 2 H), 7.02−7.17 (m, 5 H), 7.18−7.42 (m, 15 H), 7.45 (t, 1 H); 7.70, 7.77 (dd, 2 H), 7.86 (d, 1 H). $^{31}$P NMR ($CDCl_3$): $\delta$ −25.0 (s, 1P); −14.0 (s, 1P).

**2-Diphenylphosphino-3-phenylnaphtho[2,1-*b*]thiophene (3d).** Mp: 294 °C (sint. 180 °C). MS: *m*/*z* 444 ($M^+$). $^1$H NMR ($CDCl_3$): $\delta$ 7.17 (t, 1 H), 7.27−7.52 (m, 17 H), 7.71, 7.77 (dd, 2 H), 7.87 (d, 1 H). $^{31}$P NMR ($CDCl_3$): $\delta$ −24.1 (s).

**Metal Complexes 5.** Complexes **5a**,[4b] **5b**,[4b] and **5c**[8] were prepared according to already described standard procedures. Complex **5d** was prepared according to the procedure reported for the analogous BINAP complex.[9]

**Voltammetric Procedures.**[10] Voltammetries were performed in a 0.5 × $10^{-3}$ M dry acetonitrile solution, in a three-electrode cell, at 25 °C, under nitrogen, in the presence of 0.1 M tetraethylammonium perchlorate as a supporting electrolyte. The working electrode was a Pt microelectrode (0.003 $cm^2$); the counter electrode was Pt; the reference electrode was Ag/0.1 M $AgClO_4$ in acetonitrile (0.34 V vs SCE).

**Hydrogenation Procedures.** Already described hydrogenation experimental procedures were followed.[3] Specific conditions are reported in Table 1.

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**Supporting Information Available:** Elemental analysis of (±)-**3a**, (±)-**3b**, and **3d**: CD spectra ($\Delta\epsilon/\epsilon$) of (+)- and (−)-**3a**; voltammetry of **3c**; voltammetry of **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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