# (Diphenylphosphino)-biheteroaryls: the First Example of a New Class of Chiral Atropisomeric Chelating Diphosphine Ligands for Transition Metal Catalysed Stereoselective Reactions

**Tiziana Benincori,[a] Elisabetta Brenna,[a] Franco Sannicolò,*[a] Licia Trimarco,[a] Patrizia Antognazza[b] and Edoardo Cesarotti*[b]**

[a] *Dipartimento di Chimica Organica e Industriale, Università di Milano, Via Golgi 19, I-20133 Milano, Italy*
[b] *Dipartimento di Chimica Inorganica, Metallorganica e Analitica, Università di Milano, Via Venezian 21, I-20133 Milano, Italy*

Ruthenium(II) dichloride complexes with (+)- and (−)-2,2′-bis(diphenylphosphino)-4,4′,6,6′-tetramethyl-3,3′-bibenzo[*b*]thiophene (**1a**), new chiral atropisomeric heterocyclic ligands, reduce α- and β-oxoesters to α- and β-hydroxyesters with an enantiomeric purity comparable, if not higher, to that reported for binap under the same experimental conditions.

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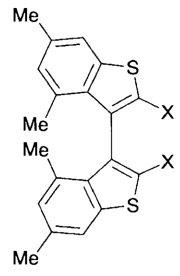
There has been much recent research on transition metal catalysts containing chiral di-terphosphine ligands for homogeneous stereoselective synthesis.[1] Current research trends are to tune the electron availability on the phosphorus atom[2] and to design ligands characterized by new geometries,[3] it being taken for granted that $C_2$ symmetry and the presence of a stereogenic axis are typical features of highly efficient di-terphosphine ligands.[4]

Surprisingly, the literature reports no examples of di-terphosphine ligands that have both the phosphorus atoms supported by the dissymmetric ($C_2$) skeleton of a biheteroaryl system showing hindered rotation at the interannular bond. We were interested to interconnect two pentatomic heteroaromatic moieties to build a ligand for the following reasons: (i) to modulate the electron availability of the phosphorus atoms simply by changing the heterocyclic system of the backbone; (ii) to evaluate the effects of the new geometry of the two interconnected pentatomic rings and compare it to known biaryl systems, all resulting from the connection of two hexatomic rings (binap, bichep and related compounds); (iii) easy and regioselective metallation reactions of heteroaromatic pentatomic compounds[5] could be extremely helpful in forming the interannular bond as well as in introducing the phosphine functions.

We report here the synthesis of optically pure (+)- and (−)-2,2′-bis(diphenylphosphino)-4,4′,6,6′-tetramethyl-3,3′-bibenzo[*b*]thiophene **1a**, and the preparation of their $Ru^{II}$ complexes which were tested in the stereocontrolled hydrogenation of some β-oxoesters.

4,6-Dimethylbenzo[*b*]thiophene[6] was brominated ($Br_2$, $CHCl_3$, 10 °C) to give 2,3-dibromo-4,6-dimethylbenzo[*b*]thiophene (mp 58 °C, yield 65%), which was debrominated to 3-bromo-4,6-dimethylbenzo[*b*]thiophene according to the method described in the literature[7] for the synthesis of 3-bromobenzo[*b*]thiophene (1 equiv. BuLi, THF, −20 °C; mp 55 °C, yield 80%). Lithiation (BuLi, THF, −78 °C), followed by the addition of an excess of anhydrous cupric chloride, gave the 4,4′,6,6′-tetramethyl-3,3′-bibenzo[*b*]thiophene **1b** (mp 126 °C, yield 44%). Lithiation of **1b** (2 equiv. BuLi, tetramethylethylenediamine, THF, −50 °C), followed by the addition of diphenylphosphinic acid chloride (2 equiv., 0 °C), gave the (±)-2,2′-bis(diphenylphosphinyl)-4,4′,6,6′-tetramethyl-3,3′-bibenzo[*b*]thiophene **1c** (mp 255–260 °C) in 44% yield.



**1a** X = $Ph_2P$
**b** X = H
**c** X = $Ph_2PO$

Racemic **1c** gave two diastereoisomeric 1 : 1 adducts with (−)-2,3-*O*,*O*′-dibenzoyl-L-tartaric acid, which were separated by fractional crystallization from an AcOEt : $CHCl_3$ (25 : 4 *v*/*v*) mixture. The less soluble diastereoisomer, mp 219 °C (decomp), $[\alpha]_D^{25}$ −153 (*c* 0.45, ethanol), obtained in a pure state after a single crystallization, was decomposed by the addition of an 0.75 mol dm$^{-3}$ NaOH solution to give (−)-**1c** as a colourless solid {$[\alpha]_D^{25}$ −256 (*c* 0.46, benzene)} which was found to be enantiomerically pure (e.e. > 99%) by chiral $^1$H NMR spectroscopy [$Eu(hfc)_3$, $CDCl_3$]. Racemic **1c** also gave two diastereoisomeric adducts with (+)-2,3-*O*,*O*′-dibenzoyl-D-tartaric acid. The less soluble diastereoisomer, mp 220 °C (decomp.), $[\alpha]_D^{25}$ +153 (*c* 0.44, ethanol) gave (+)-**1c** {$[\alpha]_D^{25}$ +244 (*c* 0.44, benzene)} which was found to be enantiomerically pure by the same NMR technique; (+)- and (−)-**1c** gave perfectly specular CD spectra (hexane). Reduction of (+)- and (−)-**1c** to (+)- and (−)-**1a**, respectively, was performed by the addition of an excess of $HSiCl_3$ (yield 70%) in refluxing xylene in the presence of triethylamine (10 h) under an argon atmosphere; final purification was performed by precipitation with methanol from a toluene solution at room temperature. Both the enantiomers were found to be enantiomerically pure by HPLC on a chiral column [Daicel Chiracel OD (250 × 4 mm, 1 × d), hexane : isopropanol 97 : 3, flow 0.2 ml min$^{-1}$]; (+)-**1a** was eluted first; mp 320 °C (decomp.) (DSC), $[\alpha]_D^{25}$ +266 (*c* 0.43, benzene) and −260 (*c* 0.44, benzene).

Chiral **1a**–ruthenium(II) dichloride complexes were prepared *in situ* from [$RuC_6H_6Cl_2$] in DMF, according to known procedures.[8]

The catalytic behaviour was tested in the hydrogenation of (pro)[1] chiral ethyl acetoacetate[9] **2a**, methyl benzoylacetate[10] **2b**, methyl phenilglioxylate[2c] **2c** and methyl pyruvate[2c] **2d** to the corresponding α- and β-hydroxyesters. To evaluate the dia-

**Table 1** Stereoselective hydrogenation of β-ketoesters catalysed by **1a**—$Ru^{II}$[a]

| Substrate | Ligand | *T*/°C | *t*/h | Yield (%) | e.e. (%) | d.e. (%) | Abs[j] |
|---|---|---|---|---|---|---|---|
| **2a** | (+)-**1a** | 70 | 2 | 95 | >99[d] | — | *R* |
| **2b**[b] | (−)-**1a** | 25 | 100 | 92 | 90[e] | — | *R* |
| **2c**[c] | (−)-**1a** | 25 | 100 | 90 | 78[f] | — | *S* |
| **2d**[c] | (−)-**1a** | 25 | 100 | 100 | 88[g] | — | *S* |
| **2e** | (+)-**1a** | 70 | 2 | 92 | >99[h]<br>(*anti*) | 86[i] | *RR* |

[a] Reactions were carried out in MeOH, S/C = $10^3$, substrate concentration 1 mol dm$^{-3}$, $pH_2$ = 10.1 mPa. [b] Solvent $CH_2Cl_2$. [c] S/C = 580. [d] $^1$H NMR $Eu(tfc)_3$. [e] Polarimetric, $[\alpha]_D^{25}$ +17.22 (*c* 4.6, EtOH).[12] [f] HPLC on Daicel Chiracel OD. [g] HPLC of (+)-MTPA ester. [h] $^1$H NMR $Eu(hft)_3$. [i] GC. [j] Absolute configuration of the major product.
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stereoselection ability of the catalyst, configurationally labile racemic 2-methoxycarbonylcyclopentanone was hydrogenated to diastereoisomeric methyl 2-hydroxycyclopentanecarboxylates.[11] In order to obtain preliminary data on the efficiency of these catalysts we selected the experimental conditions described for the same binap–Ru$^{II}$ dichloride catalysed reductions, which were carried out in parallel. The results are summarized in Table 1.

The outstanding enantio- and diastereofacial-selectivity exhibited by (+)- and (−)-**1a**–Ru$^{II}$ catalysts indicates that the new geometry induced by two interconnected pentatomic rings and the large electronic availability inherent in the thiophene ring are valuable features to be considered when designing new diterphosphine ligands. However, it will be possible to give a detailed discussion of the relationship between the Ru catalyst structure and the notable selectivity observed only when crystals suitable for X-ray investigations are available. The parallels between on enantio- and diastereo-selectivity shown by (+)-binap- and (+)-**1a**–Ru$^{II}$ complexes and by (−)-binap- and (−)-**1a**–Ru$^{II}$ complexes, together with their CD spectra, suggests that their absolute configurations should be the same, *i.e.* (*R*) and (*S*), respectively. Compound **1a** is the first example of bis(diphenylphosphino)-biheteroaryl ligands, a category which could expand rapidly given the high number of heteroaromatic rings available for such purposes.

Research on syntheses and tests of atropisomeric bis(diphenylphosphino)-bithiophenes, bipyrroles and biimidazoles is currently in progress.[13]

We wish to thank Mr B. Torretta for recording the NMR spectra and E. C. thanks Johnson Matthey for a generous gift of the RuCl$_3$ sample.

*Received, 14th December 1994; Com. 4/07632J*

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