2,2′,5,5′-Tetramethyl-4,4′-bis(diphenylphoshino)-3,3′-bithiophene: A New, Very Efficient, Easily Accessible, Chiral Biheteroaromatic Ligand for Homogeneous Stereoselective Catalysis

Tiziana Benincori,*[,†] Edoardo Cesarotti,*[,‡] Oreste Piccolo,*[,§] and Franco Sannicolò*[,||]

Dipartimento di Chimica Organica e Industriale dell'Università, via Golgi 19-20133-Milano, Italy, Dipartimento di Scienze Chimiche, Fisiche e Matematiche dell'Università dell'Insubria, via Lucini 3-22100-Como, Italy, Dipartimento di Chimica Inorganica, Metallorganica e Analitica dell'Università, via Golgi 19-20133-Milano, Italy, and Chemi S.p.A., via dei Lavoratori 54-20092-Cinisello Balsamo, Italy

Received September 30, 1999

The four-step straightforward synthesis of enantiopure (+)- and (−)-2,2′,5,5′-tetramethyl-4,4′-bis-(diphenylphoshino)-3,3′-bithiophene (tetraMe-BITIOP), a new C_2-symmetry chelating ligand for transition metals, is described, starting from 2,5-dimethylthiophene. The complexes of this electron-rich diphosphine with Ru(II) and Rh(I) were used as catalysts in some homogeneous hydrogenation reactions of prostereogenic carbonyl functions of α- and β-ketoesters, of prostereogenic carbon−carbon double bonds of substituted acrylic acids, and of *N*-acetylenamino acids. The enantiomeric excesses were found to be excellent in all the experiments and comparable with the best results reported in the literature for the same reactions, carried out under similar experimental conditions, with the metal complexes of the most popular chiral diphosphine ligands as catalysts.

Introduction

The recent trends in organic reaction development are oriented toward synthetic efficiency, which is mainly related to selectivity (chemo-, regio-, and stereoselectivity), productivity, and atom economy; it goes without saying that a reaction should be environmentally responsible by design.

Stereoselective homogeneous catalysis, promoted by complexes of transition metals with chiral ligands carrying electron-donor chelating functions, represents a methodology that perfectly meets all of these requirements.[1] In this light, the multitude of new chiral ligands for transition metals presented in recent literature[2] is amply justified when considering the enormous variety of reactions that, at least in theory, can be satisfactorily carried out in a catalytic manner.[3] The hydrogenation reactions of olefinic and carbonyl (Pro)^1-chiral and configurationally labile (Pro)^0-chiral substrates are today widely applied even for the preparation of products of industrial interest.[4] Also, the single and cascade stereoselective Heck reaction has recently attracted a great deal of attention due to its versatility and efficiency in carbon−carbon bond formation.[5] Stereoselective hydroformylation, hydrosilylation, and hydrocyanation reactions have also attained sufficient maturity levels. However, it was found that each reaction (and substrate) requires that the steric and electronic properties of the metal complex be tailored according to its needs: electron-rich diphosphines are known to give very active complexes in carbon−oxygen double-bond hydrogenation,[6] while low phosphorus electronic availability is much more favorable in olefin hydroformylation.[7] Small bite angle values are crucial for attaining high stereoselectivity levels in the former reaction, while larger values are preferable in the latter.[8]

Our previous work on chiral diphosphines characterized by an atropisomeric backbone composed of two interconnected five-membered heteroaromatic rings[9] demonstrated that the supporting heterocycle is crucial in determining phosphorus electronic availability and the geometric properties of the ligand.

† Dipartimento di Scienze Chimiche, Fisiche e Matematiche dell' Università dell'Insubria.

‡ Dipartimento di Chimica Inorganica, Metallorganica e Analitica dell'Università di Milano.

§ Chemi S.p.A.

|| Corresponding author. Dipartimento di Chimica Organica e Industriale dell'Università di Milano.

(1) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*, *I*−*III*; Springer-Verlag: Berlin, 1999 and references therein. Blaser, H.-U., Pugin, B.; Spindler, F. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann W. A., Eds.; VCH: Weinheim, 1996; p 992. Noyori, R.; Hashiguchi, S. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann W. A., Eds.; VCH: Weinheim, 1996; p 522. Sheldon, R. A. *CHEMTECH* **1994**, 38. Sheldon, R. A. *J. Mol. Catal. A* **1996**, *107*, 75.

(2) Ager, D. J.; Laneman, S. A. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3327. Enev, V.; Ewers, Ch. L. J.; Harre, M.; Nickisch, K.; Mohr, J. T. *J. Org. Chem.* **1997**, *62*, 7092.

(3) Akutagawa, S. *Appl. Catal. A: General* **1995**, *128*, 171. Kumobayashi, H. *Recl. Trav. Pays-Bas* **1996**, *115*, 201.

(4) Nugent, W. A.; RajanBabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479. Zhu, G.; Casalnuovo, A. L.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 8100. Blandin, V.; Carpentier, J.-F., Mortreux, A. *Eur. J. Org. Chem.* **1999**, 1787. Dupau, P.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron*: *Asymmetry* **1999**, *10*, 3467.

(5) Hillers, S.; Sartori, S.; Reiser, O. *J. Am. Chem. Soc.* **1996**, *118*, 2087. Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371. Trabesinger, G.; Albinati, A.; Feiken, N.; Kunz, W.; Pregosin, P. S.; Tschoerner, M. *J. Am. Chem. Soc.* **1997**, *119*, 6315. Hii, K. K.; Claridge, T. D. W.; Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *109*, 984. Tietze, L. F.; Thede, K.; Sannicolò, F. *Chem. Commun.* **1999**, 1811.

(6) Tani, K.; Suwa, K.; Tanigawa, E.; Yoshida, T.; Okano, T.; Otsuka, S. *Chem. Lett.* **1982**, 261. Tani, K.; Suwa, K.; Yamagata, T.; Otsuka, S. *Chem. Lett.* **1982**, 265. Tani, K.; Suwa, K.; Tanigawa, E.; Ise, T.; Yamagata, T.; Tatsuno, Y.; Otsuka, S. *J. Organomet. Chem.* **1989**, *370*, 203. Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, k.; Kumobayashi, H.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064.

(7) Takai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033.

(8) Dierkes, P.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519.

(9) Benincori, T.; Brenna, E.; Sannicolò, F.; Trimarco, L,; Antognazza, P.; Cesarotti, E. *J. Chem. Soc., Chem. Commun.* **1995**, 685. Antognazza, P.; Benincori, T.; Brenna, E.; Cesarotti, E.; Sannicolò, F.; Trimarco, L. *Eur. Pat.* 0770085 to Chemi S.p. A.. Benincori, T.; Brenna, E.; Sannicolò, F.; Trimarco, L,; Antognazza, P.; Cesarotti, E.; Demartin, F.; Pilati, T. *J. Org. Chem.* **1996**, *61*, 6244.

10.1021/jo991533x CCC: $19.00
Published on Web 03/09/2000

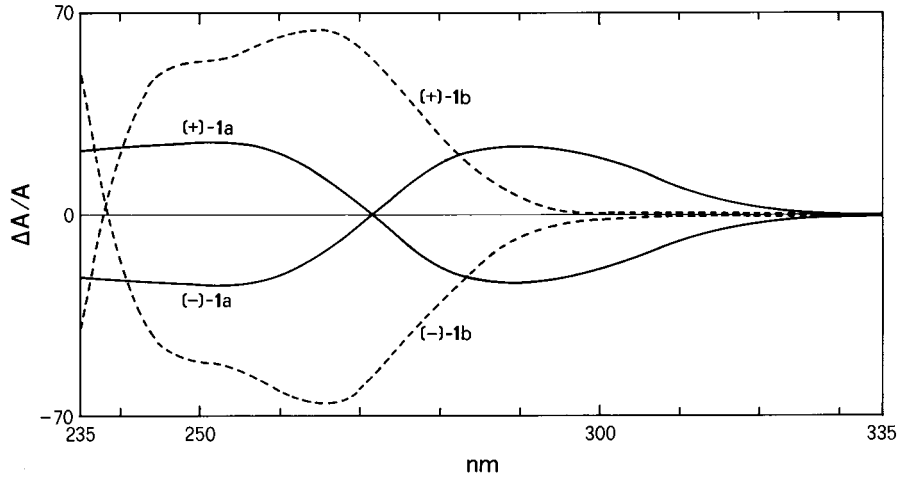
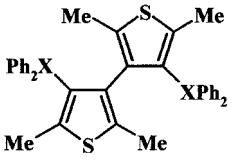


Figure 1.

The basic aim of this research was to prepare a new chiral ligand in the biheteroaromatic series endowed with high electronic density at phosphorus, low bite-angle value,[10] and tailor-made for stereoselective homogeneous hydrogenation of functionalized carbonyl and olefinic double bonds. This paper reports the synthesis and characterization of enantiopure (+)- and (−)-2,2′,5,5′-tetramethyl-4,4′-bis(diphenylphosphino)-3,3′-bithiophene (tetraMe-BITIOP) (+)-(**1a**) and (−)-(**1a**) and the preliminary results of its application as a ligand for Ru(II) and Rh(I) in homogeneous stereoselective hydrogenation of functionalized carbonyl and olefinic substrates.



1a : X = P tetraMe-BITIOP
1b : X = PO tetraMe-BITIOPO

The structural choice was dictated by the necessity of locating the diphenylphosphino group in the electron-richest position (the β-position) of an inherently electron-rich heterocyclic ring (the thiophene ring). To guarantee configurational stability to the ligand through consistent hindrance to rotation around the interanular bond, the latter necessarily had to occupy the free β' position of the thiophene ring. While the methyl group adjacent to the interanular bond gives direct contribution to the atropisomeric stability of **1a**, the other methyl group was introduced in order to develop a consistent buttressing effect on the phosphine group. This design avoiding benzocondensation turned out to be very useful, since atropisomeric diphosphines with a biphenyl backbone are known to have a definitely lower bite-angle than binaphthalene-based ones.[11]

Results and Discussion

Synthesis of racemic (±)-2,2′,5,5′-tetramethyl-4,4′-bis-(diphenylphosphinyl)-3,3′-bithiophene (tetraMe-BITIOPO) (±)-(**1b**), the phosphine oxide corresponding to **1a** on which the resolution process had to be carried out, is rather simple and involves very inexpensive starting materials and known products as intermediates. Oxidative coupling ($CuCl_2$) of 2,5-dimethyl-3-thienyllithium, obtained by transmetalation of the very easily accessible, known 3-bromo-2,5-dimethylthiophene[12] with *tert*-butyllithium, gave known 2,2′,5,5′-tetramethyl-3,3′-bithiophene[13] in a 65% yield. Dibromination of the latter with NBS, in acetic acid−chloroform solution, in the presence of hydroquinone, afforded known 4,4′-dibromo-2,2′,5,5′-tetramethyl-3,3′-bithiophene[14] in a 90% yield. Reaction with 2 equiv of butyllithium, followed by quenching of the resulting dianion with 2 equiv of chlorodiphenylphosphine, afforded the racemic diphosphine (±)-**1a**, which was oxidized in situ with diluted hydrogen peroxide to give the diphosphine oxide (±)-**1b**, in an 85% yield.

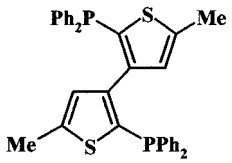
Resolution was performed by fractional crystallization from tetrahydrofuran of the diastereomeric adducts of **1b** with (+)- and (−)-dibenzoyltartaric acids. Alkaline decomplexation of the adducts afforded 90% enantiomerically enriched antipodes, which were obtained in their enantiopure forms by crystallization from a 1:1 benzene−hexane mixture, from which the racemate separates first. Enantiomeric purity was checked by chiral HPLC.[15] (+)-**1b**: $[\alpha]^{25}_D = +66$ ($c = 0.49$, C_6H_6). (−)-**1b**: $[\alpha]^{25}_D = -68$ ($c = 0.50$, C_6H_6). The CD spectra of (+)-**1b** and (−)-**1b** are reported in Figure 1. Reduction of enantiomerically pure phosphine oxides **1b** to phosphines **1a** was performed by reaction with an excess of trichlorosilane in the presence of triethylamine in refluxing toluene solution. Dextrorotatory (+)-**1b** gave levorotatory (−)-**1a**, $[\alpha]^{25}_D = -27$ ($c = 0.48$, C_6H_6), and levorotatory (−)-**1b** gave dextrorotatory (+)-**1a**, $[\alpha]^{25}_D = +27$ ($c = 0.51$, C_6H_6). Enantiomeric purity was checked by chiral HPLC, performed on the phosphine oxides, which were obtained by hydrogen peroxide oxidation. Alternatively, for the same purpose, ^{31}P NMR spectroscopy could be employed. The spectra of the diastereomeric aminopalladium complexes of (+)-**1a** and (−)-**1a** with enantiopure, commercially available di-μ-chlorobis[(*S*)-dimethyl(α-methylbenzyl)-aminato-C^2N]palladium(II) were prepared directly in an NMR tube according to a known method[16] and showed

(10) Bonifacio, F.; Piccolo, O. *Chiratech '97*, Nov 11−13, 1997, Philadelphia, PA.
(11) Zhang, X. *ChiraSource '99*, Nov 15−17, 1999, Philadelphia, PA.
(12) Yoshida, K.; Saeki, T.; Fueno, T. *J. Org. Chem.* **1971**, *36*, 3673. Kannappan, V.; Nanjan, M. J.; Ganesan, R. *Indian J. Chem. Sect. A.* **1980**, 1183.
(13) v. Steinkopf, W.; Barlang, T.; Petersdorff, H. J. *Justus Liebigs Ann. Chem.* **1940**, *543*, 119. Davies, A. G.; Julia, L.; Yazdi, S. N. *J. Chem. Soc., Perkin Trans. 2* **1989**, 239.
(14) Hakansson, R. *Acta Chem. Scand.* **1971**, 1313.
(15) Ferretti, R.; Gallinella, B.; La Torre, F.; Zanitti, L.; Bonifacio, F., Piccolo, O. *J. Chromatogr. A* **1998**, *795*, 289.

well-separated AB systems at 34.3−8.80 and 33.3−8.30 ppm, respectively. The signals attributable to one diastereoisomer were completely absent in the spectrum of the other. The CD spectra of (+)-**1a** and (−)-**1a** are reported in Figure 1.

Absolute configuration to the antipodes of **1a** and **1b** was assigned by comparison of their CD curves with those shown by other biheteroaromatic diphosphines, including the one for which absolute configuration was known through single-crystal X-ray diffractometric analysis:[17] the *R* configuration was assigned to (+)-**1b** and (−)-**1a**, while the *S* configuration was assigned to (−)-**1b** and (+)-**1a**. This is further supported by the correlation between the optical rotatory power sign of the ligand and the absolute configuration of the hydrogenation products.

Evaluation of electronic availability at phosphorus in **1a** was effected as usual by cyclic voltammetry under standardized experimental conditions.[18] The electrochemical oxidative potential of **1a** was found to be 0.57 V, which is, so far, the lowest value in the whole class of biheteroaromatic diphosphines. TetraMe-BITIOP, therefore, not only is the most electron-rich ligand in that series but it is also more electron-rich than BINAP (0.63 V). Such a low value of electrochemical oxidative potential was mainly attributed to the location of the diphenylphosphino groups on the thiophene ring. The phosphine groups in the β position are expected to be more electron-rich than those bonded to α carbons, where sulfur exerts more consistent inductive effects. To give clearer evidence of the effects on the electronic properties of phosphorus related to its position on a given heterocyclic ring, we synthesized 2,2′-bis(diphenylphosphino)-5,5′-dimethyl-3,3′-bithiophene (diMe-BITIOP) (**2**), even though we were aware that it could not be configurationally stable.



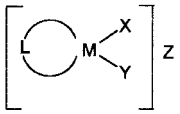
2

diMe-BITIOP

Synthesis was achieved by double lithiation of known 2,2′-dimethyl-3,3′-bithiophene,[19] followed by reaction with 2 equiv of chlorodiphenylphosphine. The electrochemical oxidative potential of **2** was found to be 0.70 V. The comparison of the redox potentials of **1a** and **2** confirms that phosphine groups bound to the α position of a thiophene ring are definitely more electron-poor than those situated in β. The observed difference of 0.13 V cannot be exclusively attributed to the extra methyl group present on the thiophene ring of **1a**, since the decrease in the electrochemical oxidative potential following the introduction of a second methyl group on the 3-methylthiophene ring is known to be 0.10 V.[20]

It is evident that when designing biheteroaromatic diphosphines it is possible to fine-tune the electronic properties on phosphorus either by changing the supporting heterocycle or the position of phosphorus on it.

Asymmetric Hydrogenation of Functionalized Carbonyl and Olefinic Substrates. Catalytic hydrogenation experiments were carried out on substrates that are in standard use for evaluation of the catalytic activity (kinetics) and stereoselection ability of all new chiral ligands appearing in the literature. Ruthenium(II) complexes **3a**, **3b**, and **3c** were used in the reduction of α-

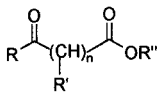


3

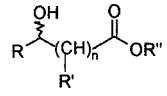
L = tetraMe-BITIOP

a:	M = Ru	X = Y = Cl	
b:	M = Ru	X = p-cymene	Y = Z = I
c:	M = Ru	X = benzene	Y = Z = Cl
d:	M = Ru	X = Y = methallyl	
e:	M = Rh	X, Y = COD	Z = BF_4

and β-oxoesters **4a**−**h** to the corresponding hydroxyesters **5a**−**h**. Methallyl groups were used as ancillary ligands of ruthenium(II) (complex **3d**) in the hydrogenation of acrylic acid derivatives **6a**,**b** to tiglic (**7a**) and atropic (**7b**) acids. Rhodium(I) complex **3e** was employed in the

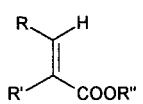


4

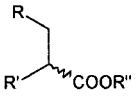


5

a:	n = 1	R = CH_3	R' = H	R" = C_2H_5
b:	n = 1	R = CH_3	R' = Cl	R '' = C_2H_5
c:	n = 1	R = CF_3	R' =H	R" = C_2H_5
d:	n = 1	R = C_6H_5	R' = H	R" = C_2H_5
e:	n = 1	R = CH_3	R' = CH_2-NH-CO-C_6H_5	R" = C_2H_5
f:	n = 1	R-R' = $(CH_2)_3$		R" = CH_3
g:	n = 0	R = C_6H_5	R' = H	R" = CH_3
h:	n = 0	R = C_6H_5-$(CH_2)_2$-	R' = H	R" = C_2H_5



6



7

a:	R = R" = H	R' = C_6H_5	
b:	R = R' = CH_3	R" = H	
c:	R = C_6H_5	R' = NH-CO-CH_3	R" = H
d:	R = α-Naphth	R' = NH-CO-CH_3	R" = CH_3

hydrogenation of the carbon−carbon double bond of *N*-acetyl-α-enamino acids or esters **6c**,**d** to the corre-

(16) Roberts, K. N.; Wild, S. B. *J. Chem. Soc., Dalton Trans.* **1979**, 2015.

(17) Antognazza, P.; Benincori, T.; Mazzoli, S.; Sannicolò, F.; Zotti, G. *Phosphorus, Sulfur, Silicon* **1999**, *146*, 405.

(18) Benincori, T.; Brenna, E.; Sannicolò, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E.; Zotti, G. *J. Organomet. Chem.* **1997**, *529*, 445.

(19) Gronowitz, S.; Frostling, H. *Tetrahedron Lett.* **1961**, *17*, 607.

Table 1. Asymmetric Hydrogenation of α- and *β*-Ketoesters

substrate	catalyst[a]	solvent	additive	*P* (kg/cm^2)	S/C	*T* (°C)	*t* (h)[b]	ee[c] (de) (%)	confgn
4a	(+)-**3a**	EtOH		100	1000	40	3	94	*S*
4a	(+)-**3a**	EtOH		100	1000	70	1	98	*S*
4a	(+)-**3b**	EtOH		50	1000	30	24	97	*S*
4a	(+)-**3b**	EtOH		25	1000	30	68	97	*S*
4b	(+)-**3d**	C_7H_{16}		100	1000	80		94 (82)[d]	
4c	(+)-**3b**	EtOH		40	200	110	1	85	*R*
4d	(−)-**3a**	MeOH,H_2O		100	257	45	2	93[c]	*S*
4e	(−)-**3b**	CH_2Cl_2	RSO_3H	100	200	50	0.3	99 (94)	3*S*,2*R*
4f	(+)-**3a**	MeOH		100	1000	80		50 (77)[d]	*S*,*S*
4f	(+)-**3a**	MeOH	CF_3COOH	100	1000	80		99 (84)[d]	*S*,*S*
4f	(+)-**3b**	MeOH		100	1000	70		62 (88)[d]	*S*,*S*
4f	(+)-**3b**	MeOH	CF_3COOH	100	1000	80		99 (88)[d]	*S*,*S*
4g	(+)-**3c**	MeOH	HBF_4	96	516	25	75	89	*R*
4h	(+)-**3c**	EtOH, H_2O	HBF_4	100	462	50		91	*S*

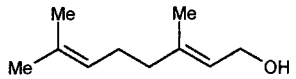
[a] The optical rotatory power sign refers to that of the corresponding phosphine. [b] At 95% conversion. [c] Unless otherwise specified, ee and dd were determined by chiral HPLC analysis. [d] Chiral GC analysis.

Table 2. Asymmetric Hydrogenation of Olefinic Substrates

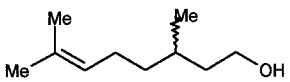
sub-strate	cata-lyst[a]	solvent	*P* (kg/cm^2)	S/C	*T* (°C)	t (h)[b]	ee[c] (%)	confgn
6a	(−)-**3d**	MeOH	50	160	20		94[d]	*R*
6b	(−)-**3d**	MeOH	10	3000	25		94[d]	*R*
6c	(−)-**3e**	EtOH	3	90	25		87	*R*
6d	(−)-**3e**	THF/MeOH	20	80	10	18	94	*R*
8	(+)-**3a**	MeOH	100	160	25	0.5	92[e]	*R*

[a] The optical rotatory power sign refers to that of the corresponding phosphine. [b] At 95% conversion. [c] Unless otherwise specified, ee was determined by chiral HPLC analysis. [d] Chiral GC on the methyl ester (diazomethane). [e] Determined by polarimetric analysis.

sponding *N*-acetyl-α-amino acids or esters **7c**,**d**. Complex **3a** was also employed in the hydrogenation of the allylic double bond of geraniol (**8**) to citronellol (**9**).



8



9

Table 1 summarizes the stereoselection data found in carbon−oxygen double bond reduction of α- and *β*-ketoesters and the experimental conditions.

Table 2 summarizes the enantioselection data found in carbon−carbon double bond reduction and the experimental conditions.

It appears that the enantiofacial recognition ability of tetraMe-BITIOP is very high, comparable to that exhibited by well-known ligands, like BINAP and DuPHOS. Also, from the standpoint of reaction rate, in experiments comparing tetraMe-BITIOP to BINAP, it was observed that lower reaction times were required due to its greater electronic availability at phosphorus. Furthermore, under extremely fast reaction conditions, variations in enantiomeric excess were observed, as if the concentration of available hydrogen were the limiting factor for hydrogenation. A more detailed kinetic analysis will be reported elsewhere.

It is interesting to note that the use of acid cocatalysts significantly improves both enantiomeric and diastereomeric excesses in hydrogenation reactions of *β*-ketoesters **4e** and **4f**, which are chiral substrates for which kinetic resolution is possible, since they have a configurationally labile stereocenter in α position to the reactive carbon.

Conclusions

TetraMe-BITIOP (**1**), presented in this paper, is one of the most efficient diphosphine chiral chelating ligands available today for use in enantioselective homogeneous hydrogenation. A great advantage offered by tetraMe-BITIOP over its competitors is its very good synthetic accessibility: this ligand can be easily obtained in 10 g batches through a simple and reliable six-step synthetic scheme (including resolution), carried out with an approximately 30% overall yield starting from inexpensive 2,5-dimethylthiophene. Attempts are currently under way to improve yields and to simplify the synthetic scheme so as to make it suitable for industrial development.

The results of this research also provide further evidence of a property peculiar to the class of five-membered biheteroaromatic diphosphines, that is the possibility of modulating the electronic availability on phosphorus. Electronic tuning can be done either by choosing heterocyclic rings with different inherent electronic richness, or, given the same heterocycle, by locating the phosphino groups in different positions with respect to the heteroatom(s).

Even though each substrate requires a custom-designed catalyst and the reaction conditions need to be adjusted to obtain cost-effective procedures, we are convinced that tetraMe-BITIOP can be successfully utilized and give significant results even on an industrial scale.[21]

Experimental Section

Preparation of 4,4′-Bis(diphenylphosphinyl)-2,2′,5,5′-tetramethyl-3,3′-bithiophene (±)-1b. BuLi (3.8 mL, 1.6 M solution in hexane, 6.08 mmol) was dropped into a solution of 4,4′-dibromo-2,2′,5,5′-tetramethyl-3,3′-bithiophene (1.15 g, 3.0 mmol) in THF (30 mL) at −60 °C under N_2. After 10 min of stirring, diphenylphosphinous chloride (1.1 mL, 6.13 mmol) was added; the mixture was stirred for 1 h, and the temperature was allowed to warm to room temperature. The mixture was concentrated under reduced pressure and the residue treated with water and extracted with CH_2Cl_2. The organic

(20) Waltman, R. J.; Bargon, J.; Diaaz, A. F. *J. Phys. Chem.* **1983**, *87*, 1459. Tourillon, G.; Garnier, F. *J. Electroanal. Chem.* **1984**, *161*, 51.

(21) Chemi S.p. A. has already employed this ligand in hydrogenation reactions carried out on a 50−200 kg scale level.

(22) Schenck, T. G.; Downes, J. M.; Milne, C. R. C.; Mackenzie, P. B.; Boucher, H.; Whelan, J.; Bosnich, B. *Inorg. Chem.* **1985**, *24*, 2334.

layer was treated with H_2O_2 (10 mL, 35%) at 0 °C. The mixture was stirred for 1 h at 0 °C and for 1 h at room temperature and then diluted with water. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, eluant AcOEt/CH_2Cl_2/Et_3N 3:7:0.1) provided pure **(±)-1b** (98%): mp 140 °C; ^{1}H NMR ($CDCl_3$) δ 7.6 (m, 20H), 1.95 (d, 6H), 1.65 (s, 6H); ^{31}P NMR ($CDCl_3$) δ 21.19; mass spectrum *m*/*z* 622 (M^+). Anal. Calcd for $C_{36}H_{32}S_2P_2O_2$: C, 69.44; H, 5.18. Found: C, 69.23; H, 5.09.

Resolution of 4,4′-Bis(diphenylphosphinyl)-2,2′,5,5′-tetramethyl-3,3′-bithiophene (±)-1b with (−)- or (+)-2,3-*O*,*O*′-Dibenzoyltartaric Acid (DBTA). A mixture of (±)-**1b** (12.5 g) and monohydrate (−)-DBTA (7.6 g) was dissolved in THF (150 mL), refluxed for a few minutes, and allowed to stand at room temperature for 24 h. An adduct between (+)-**1b** and (−)-DBTA was collected, and the filtrate was stored for recovery of (−)-**1b**. The adduct was dissolved into warm THF (450 mL), and a pure adduct was collected [8.76 g, mp 159−172 °C (DEC), $[\alpha]^{25}_D = -36.9$ (*c* = 0.49, benzene)] after standing for 10 days. The adduct was treated with 0.75 N NaOH solution, and the mixture was extracted exhaustively with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give a solid that was crystallized from a hexane/benzene 1:1 mixture to give (+)-**1b** [2.1 g, mp 236 °C, $[\alpha]^{25}_D = +62$ (*c* = 0.49, benzene)]. The mother liquors from the first resolution step were concentrated to dryness to give a solid that was treated with a 0.75 N NaOH solution and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4), and concentrated in vacuo to give (−)-**1b**, which was crystallized from hexane/benzene 1:1 [1.2 g, mp 236 °C, $[\alpha]^{25}_D = -62$ (*c* = 0.49, benzene)].

Preparation of (+)- and (−)-4,4′-Bis(diphenylphosphino)-2,2′,5,5′-tetramethyl-3,3′-bithiophene [(+)- and (−)-1a]. In a three-necked flask equipped with a thermometer and a reflux condenser connected to an argon inlet tube were placed (+)-**1b** (0.49 g), dry xylene (15 mL), trichlorosilane (0.52 mL), and triethylamine (0.72 mL). The mixture was stirred and heated at 100 °C for 1 h and then at 140 °C for 3 h. After cooling to room temperature, the mixture was concentrated in vacuo, and the residue was treated with water and extracted with CH_2Cl_2. The residue was treated with methanol, and the precipitate was collected to give (−)-**1a** [0.29 g, mp 178 °C and $[\alpha]^{25}_D = -27.4$ (*c* = 0.51, benzene)].

(−)-**1b** was reduced to (+)-**1a** by following the same procedure described above for (+)-**1b** [mp 179 °C, $[\alpha]^{25}_D = +27.4$ (*c* = 0.51, benzene)]: ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 20 H), 6.85 (s, 2 H), 2.40 (s, 6 H); ^{31}P NMR ($CDCl_3$) δ −24.98; mass spectrum *m*/*z* 590 (M^+). Anal. Calcd for $C_{36}H_{32}S_2P_2$: C,73.20; H, 5.46. Found: C,73.04; H, 5.27.

Preparation of 2,2′-Bis(diphenylphosphino)-5,5′-dimethyl-3,3′-bithiophene (2). BuLi (3.8 mL, 1.6 M solution in hexane, 6.08 mmol) was dropped into a solution of 5,5′-dimethyl-3,3′-bithiophene (0.58 g, 3.0 mmol) in THF (30 mL) at −60 °C under N_2. After 10 min of stirring, diphenylphosphinous chloride (1.1 mL, 6.13 mmol) was added; the mixture was stirred for 1.5 h, and the temperature was allowed to warm to room temperature. The mixture was concentrated under reduced pressure and the residue treated with water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was treated with diisopropyl ether to give **2** (80%): mp 236−239 °C; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 20 H), 6.85 (s, 2H), 2.40 (s, 6 H); ^{31}P NMR ($CDCl_3$) δ −24.98; mass spectrum *m*/*z* 562 (M^+). Anal. Calcd for $C_{34}H_{28}S_2P_2$: C, 72.58; H, 5.02. Found: C, 72.47; H, 5.01.

Preparation of [(+)- and (−)-TetraMe-BITIOP]$RuCl_2$ (3a). To a Schlenk tube charged with (+)- or (−)-tetraMe-BITIOP (2.3×10^{-2} mmol) and $[RuCl_2(C_6H_6)]_2$ (1.15×10^{-2} mmol) was added freshly distilled argon-degassed DMF. The mixture was stirred at 100 °C for 15 min. The resulting orange solution was cooled to 50 °C and concentrated under reduced pressure to give **3a**. The ruthenium complex residue was utilized without further purification: ^{31}P NMR ($CDCl_3$) δ 69.4 (d, *J* = 53 Hz), 62.1 (d, *J* = 38 Hz), 60.2 (d, *J* = 42 Hz), 58.7 (d, *J* = 42 Hz), 58.0 (d, *J* = 42 Hz), 55.3 (d, *J* = 40 Hz), 54.3 (d, *J* = 42 Hz), 53.9 (d, *J* = 47 Hz).

Preparation of (+)- and (−)-[(TetraMe-BITIOP)Ru(*p*-cymene)I]I (3b). (+)- or (−)-tetraMe-BITIOP (0.024 g), [Ru-(p-cymene)I_2]$_2$ (0.015 g), methanol (3 mL), and CH_2Cl_2 (8 mL) were stirred in a Schlenk tube under argon at 50 °C for 1.5 h. The solution was concentrated under reduced pressure to give **3b** as a red solid that was used as catalyst in hydrogenation reactions without further purification: ^{31}P NMR ($CDCl_3$) δ 38.0 (d, *J* = 63 Hz), 15.3 (d, *J* = 63 Hz).

Preparation of (+)- and (−)-[(TetraMe-BITIOP)Ru-(C_6H_6)Cl]Cl (3c). (+)- or (−)-tetraMe-BITIOP (0.045 g), $[(C_6H_6)RuCl_2)_2$ (0.019 g), ethanol (10 mL), and benzene (1.3 mL) were stirred in a Schlenk tube under argon for 1 h at 50−60 °C. The orange solution was evaporated under reduced pressure to give **3c** as an orange-yellow solid that was used in the asymmetric catalysis experiments without further purification: ^{31}P NMR ($CDCl_3$) δ 22.5 (d, *J* = 62 Hz), 38.7 (d, *J* = 62 Hz).

Preparation of (−)-[(TetraMe-BITIOP)Ru Bis(2-methallyl)] [(−)-3d]. (−)-TetraMe-BITIOP (0.0104 g), [(COD)Ru bis(2-methallyl) (0.0054 g), and toluene (5 mL) were stirred at 110 °C for 2 h. The solution was concentrated under reduced pressure to give **3d.** The Ru complex residue was used in asymmetric hydrogenation without further purification: ^{31}P NMR ($CDCl_3$) δ 36.25.

Preparation of (−)-[(tetraMe-BITIOP)Rh(COD)]BF_4 [(−)-3e]. A solution of $[Rh(COD)_2]BF_4$[21] (0.314 g) and (−)-tetraMe-BITIOP (0.457 g) in CH_2Cl_2 (18 mL) was stirred under argon at room temperature for 1 h. The solvent was partially removed (10 mL) under reduced pressure, and THF (15 mL) first, then hexane (20 mL), were added. The yellow-orange precipitate was filtered under argon and used as catalyst in hydrogenation reactions without further purification: ^{31}P NMR ($CDCl_3$) δ 20.51 (d, *J* = 145.8 Hz).

Hydrogenation Reactions. In a typical experiment (Table 1, entry 1), a solution of ethyl 3-oxobutanoate (**4a**) (20 mmol) and (+)-**3a** (0.020 mmol) in methanol (10 mL), previously degassed with argon, was loaded with a syringe into a 100 mL Parr autoclave. Hydrogen was introduced (100 kg/cm^2), and the solution was stirred at 70 °C for 30 min. The autoclave was cooled, the hydrogen pressure released, the solvent evaporated, and the residue distilled (17 mmHg) to give ethyl (*S*)-(+)-3-hydroxybutanoate (**5a**) (98%).

Acknowledgment. Dr. P. Antognazza, Dr. S. Araneo, Dr. F. Bonifacio, Dr. C. Crescenzi, Dr. G. De Iase, Dr. G. Melato, Dr. S. Tollis, Dr. U. Tuan, and Dr. A. Turri are acknowledged for their contribution to the experimental success of this project. Also acknowledged is Dr. G. Zotti (CNR-IPELP, Padua, Italy) for CV experimentation. This work was supported in part (T.B., F.S.) by Chemi S.p.A., holder of the patents for the synthesis and use of all biheteroaryl-diphosphine ligands, and MURST COFIN 1998/99 project (9803153701).

JO991533X