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Expanding the Family of Phospholane-Based Ligands: 1,2-Bis(2,5-diphenylphospholano)ethane

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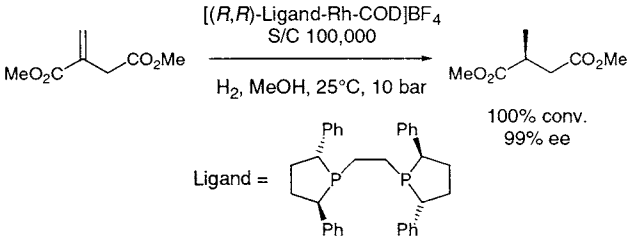
ABSTRACT



1,2-Bis(2,5-diphenylphospholano)ethane (Ph-BPE) has been synthesized for the first time through employment of an undemanding synthetic pathway. The new ligand exhibits enhanced activity and selectivity over the existing members of the BPE ligand family in rhodium-catalyzed asymmetric hydrogenation.

Asymmetric hydrogenation using transition metal complexes represents one of the most effective methods for the synthesis of optically active compounds.[1] The complexes of the 1,2-bis(2,5-dialkylphospholano)ethane (BPE) **1** and 1,2-bis(2,5-dialkylphospholano)benzene (DuPHOS) **2** ligands (Figure 1), first reported by Burk,[2] have proven to be invaluable in this field. These ligands, featuring a 2,5-disubstituted phospholane structural motif, have essentially solved the problem of the asymmetric hydrogenation of dehydroamino acids.[3] Furthermore, the combination of robustness, high activity, and excellent selectivity renders these ligands suitable for large-scale industrial application.[4] The practicality of phospholane ligands is confirmed by the ever-growing number of structural analogues reported in the literature.[5]

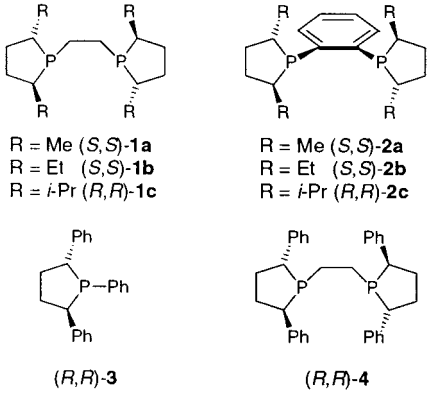


Figure 1. 2,5-Disubstituted phospholane ligands.

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(5) (a) Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Stürmer, R.; Börner, A. *J. Org. Chem.* **1998**, *63*, 8031. (b) Yan, Y-. Y.; RajanBabu, T. V. *J. Org. Chem.* **2000**, *63*, 900. (c) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *63*, 3489.

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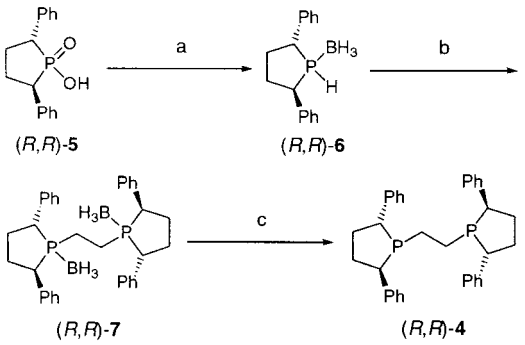
The possibility of accessing phospholane units with different substituents at the 2- and 5-positions has allowed the steric fine-tuning necessary to obtain the best results over a wide range of substrates.[6] For example, Me-DuPHOS and Et-DuPHOS (**2a** and **2b**, respectively) usually provide the best rhodium catalysts for the asymmetric hydrogenation of dehydroamino acids[3] and β-monosubstituted itaconates,[7] while Me-BPE **1a** is the ligand of choice for the rhodium-catalyzed hydrogenation of β,β-disubstituted itaconates.[7]

An obvious modular extension to the 2,5-disubstituted bisphospholane family of ligands are the aryl analogues. However, these ligands have so far proved to be elusive.

The preferred method for the preparation of the dialkyl phospholanes is the reaction of an appropriately substituted cyclic sulfate, derived from the corresponding enantiomerically pure diol, with a lithiated phosphide.[3] However, with diaryl cyclic sulfates and dimesylates elimination or racemization is observed. The avoidance of such problems in the formation of a 2,5-diphenyl phospholane unit has been addressed in recent disclosures by Fiaud and co-workers on the synthesis of 1-phenyl-2,5-diphenylphospholane **3**.[8] Using these key publications as impetus, we endeavored to synthesize the chiral phospholane ligand 1,2-bis(2,5-phenylphospholano)ethane (Ph-BPE) **4** from phospholanic acid **5**. Herein, we report the synthesis of the Ph-BPE ligand and its use in rhodium-catalyzed asymmetric hydrogenation.

The enantiomerically pure phospholanic acid **5** was prepared and resolved according to the method reported by Fiaud.[8] Scheme 1 depicts the series of steps that led us from

Scheme 1. Preparation of the Ph-BPE Ligand[a]



[a] Reagents and conditions: (a) (i) $PhSiH_3$, toluene, 110 °C, 16 h; (ii) $BH_3{\cdot}SMe_2$, THF, from 0 °C to rt (95%). (b) *n*-BuLi, THF, from −78 °C to rt, 30 min, then $TsOCH_2CH_2OTs$, THF, rt, 40 h (69%). (c) $HBF_4{\cdot}OMe_2$, CH_2Cl_2, rt, 16 h (92%).

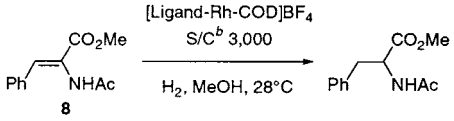
phospholanic acid **5** to Ph-BPE **4**. Phospholanic acid **5** was reduced using $PhSiH_3$[9] and subsequently treated with $BH_3{\cdot}SMe_2$ to afford borane adduct **6**. Synthesis of the BPE framework was then accomplished by deprotonation of adduct **6** with *n*-BuLi and reaction with 1,2-ethylene ditosylate to give bisphospholane **7**. No formation of the unwanted *meso*-compound was detected at this stage. The formation of Ph-BPE **4**[10] was finally realized by deprotection of **7** with HBF_4.[11] The optical purity of Ph-BPE **4** was confirmed by oxidation of a sample to the corresponding phosphino-oxide and analysis by chiral HPLC.[12]

This pathway represents a reversal of the established strategy for the synthesis of bidentate phospholane-based ligands. The phospholane ring is constructed as a distinct entity prior to attachment to the backbone rather than being assembled at the end of the synthesis.

With the long sought after Ph-BPE ligand in hand, we were able to test its performance in homogeneous asymmetric hydrogenation and compare it with the other members of the BPE ligand family. To this end, the rhodium complex [(*R*,*R*)-Ph-BPE Rh COD]BF_4 was prepared by reaction of the free ligand with $[Rh(COD)_2]BF_4$ and tested against a series of substrates.

Hydrogenation of methyl acetamidocinnamate **8** at a molar substrate-to-catalyst ratio (S/C) of 3000 immediately indicated that substantially improved activity and selectivity is achieved with the Ph-BPE rhodium catalyst compared with the other BPE rhodium catalysts (Table 1). The level of selectivity (99% ee) is comparable to that obtained with the best DuPHOS ligands.[13] Surprisingly, *i*-Pr-BPE gave much lower activity than expected.

Table 1. Asymmetric Hydrogenation of Methyl Acetamido-cinnamate Using Rhodium BPE Catalysts[a]



entry	ligand	time (min)	conversion (%)[c]	ee (%)[c]
1	(*R*,*R*)-**1a**	90	100	85 (*R*)[d]
2	(*R*,*R*)-**1b**	120	100	88 (*R*)
3	(*S*,*S*)-**1c**	840	83	94 (*R*)
4	(*R*,*R*)-**4**	75	100	99 (*S*)

[a] Reactions were performed simultaneously in an Argonaut Endeavor reaction vessel with 1.5 M solutions of substrate in MeOH at 28 °C under 10 bar hydrogen pressure. [b] Molar substrate-to-catalyst ratio. [c] Conversion and enantiomeric excess were determined by chiral GC. [d] Product stereochemistry and enantioselectivity are consistent with that stated in ref 2b.

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(7) Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Gerosa, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1931.

(8) (a) Guillen, F.; Fiaud, J-. C. *Tetrahedron Lett.* **1999**, *40*, 2939. (b) Guillen, F.; Rivard, M.; Toffano, M.; Legros, J-. Y.; Daran, J-. C.; Fiaud, J-. C. *Tetrahedron* **2002**, *58*, 5895.

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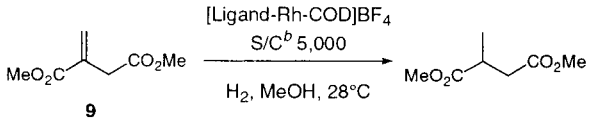
(10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (m, 2H), 0.96 (m, 2H), 1.76−1.86 (m, 2H), 2.05−2.15 (m, 2H), 2.27 (m, 2H), 2.48 (m, 2H), 2.95 (m, 2H), 3.59 (m, 2H), 7.08 (m, 6H), 7.16 (m, 4H), 7.21 (m, 6H), 7.30 (m, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.01; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.45 (dd, J_{CP} = 36.0 Hz, J_{CCP} = 27.1 Hz, bridge CH_2), 31.92 (s, ring CH_2), 37.38 (s, ring CH_2), 46.15 (m, ring CH), 50.57 (m, ring CH), 125.75 (s), 125.83 (s), 127.25 (s), 127.86 (m), 128.30 (s), 128.53 (s), 138.33 (m, *ipso*-C_{Ar}), 144.65 (m, *ipso*-C_{Ar}); HRMS (EI) *m*/*z* calcd for $C_{34}H_{36}P_2$ 506.2292, found 506.2269; $[\alpha]_D$ = −174.9 (*c* = 0.3, CH_2Cl_2).

(11) McKinstry, L.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 7655.

(12) Chialpak AD-H (250 × 4.6 mm), heptane/EtOH 80/20, 1 mL/min, 25°C, detection by UV at 210 nm: 9.5 min (*S*,*S*), 15.2 min (*R*,*R*), 22.9 min (*meso*); >98% ee.

The same trend was observed in the hydrogenation of dimethyl itaconate **9** (Table 2). The reaction was tested at

Table 2. Asymmetric Hydrogenation of Dimethyl Itaconate Using Rhodium BPE Catalysts[a]



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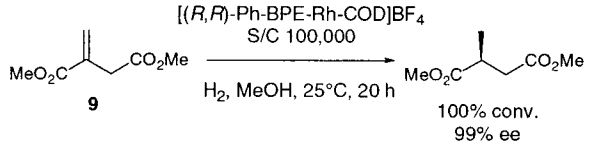
entry	ligand	time (min)	conversion (%)[c]	ee (%)[c]
1	(*R*,*R*)-**1a**	30	100	91 (*R*)
2	(*R*,*R*)-**1b**	30	100	95 (*R*)
3	(*R*,*R*)-**1c**	840	61	50 (*S*)
4	(*R*,*R*)-**4**	25	100	99 (*S*)
5[d]	(*R*,*R*)-**4**	10	100	99 (*S*)

[a] Reactions were performed simultaneously in an Argonaut Endeavor reaction vessel with 2.5 M solutions of substrate in MeOH at 28 °C under 10 bar hydrogen pressure. [b] Molar substrate-to-catalyst ratio. [c] Conversion and enantiomeric excess were determined by chiral GC. [d] Reaction was run at a S/C of 10 000 in an impeller-stirred 300 mL reaction vessel; more efficient stirring provides increased mass-transfer.

S/C = 5000, and again the Ph-BPE Rh catalyst was found to be the most active and by far the most selective of the BPE-based catalysts. Low selectivity and low activity were attained using *i*-Pr-BPE as the ligand. The high activity of the Ph-BPE rhodium catalyst was further demonstrated by reaction with dimethyl itaconate **9** at S/C = 100 000. The hydrogenation of 50 g of substrate went to completion overnight with an ee of 99% (Scheme 2).

Scheme 2. Asymmetric Hydrogenation of Dimethyl Itaconate with Rhodium Ph-BPE **4**[16]



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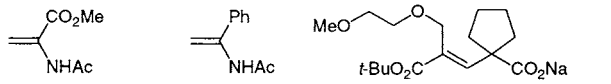
The scope of the Ph-BPE rhodium catalyst's utility was further probed by hydrogenation of other substrates (Figure 2). The hydrogenation of both methyl 2-acetamidoacrylate

(13) Under the same conditions Me-DuPHOS produced an ee of 98%, while Et-DuPHOS gave an ee > 99%.



10
S/C 5,000
100% conv.
99% ee

11
S/C 5,000
100% conv.
99% ee

12
S/C 1000
100% conv.
>98% ee

Figure 2. Further hydrogenation substrates screened against Ph-BPE **4**.[17]

10 and *N*-(1-phenylvinyl)acetamide **11** gave 99% ee with full conversion. The Candoxatril precursor **12** was chosen as an example of a substrate where asymmetric hydrogenation has proved to be industrially valid.[14] The ee for this hydrogenation represents an improvement over the selectivity obtained previously with other rhodium BPE catalysts and is comparable with DuPHOS-based catalysts.[15]

In summary, we have reported the first preparation of the ligand Ph-BPE **4** that exploits a synthetic route that conceptually differs from the established BPE ligand synthesis. The replacement with phenyl groups of the alkyl substituents at positions 2 and 5 of the phospholane ring has produced in all of the cases examined a substantial increase in both the activity and the selectivity obtainable in rhodium-catalyzed asymmetric hydrogenation. The synthesis of other phenylphospholane-based bisphosphine ligands is under way and will be reported in due course.

Acknowledgment. We thank Catherine Rippe, Natasha Cheeseman, Jonathan Hill, and Brendan Mullen of Chirotech's analytical team for their skilled technical assistance. We also thank Dr. Steve Challenger and Pfizer Ltd., for their supply of the Candoxatril precursor.

Supporting Information Available: Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) [(*S*,*S*)-Me-BPE Rh COD]BF_4 80% ee; [(*S*,*S*)-Et-BPE Rh COD]BF_4 97% ee; [(*S*,*S*)-*i*-Pr−BPE Rh COD]BF_4 92% ee; see ref 14 for further details.

(16) Reactions were performed in a thermostated 300 mL reaction vessel with 50 g of substrate in MeOH at 25°C under 10 bar hydrogen pressure. The substrate was used as bought from Acros, 97% purity. S/C denotes molar substrate-to-catalyst ratio. Conversion and enantiomeric excess were determined by chiral GC.

(17) Reactions were performed in a 50 mL reaction vessel with 0.8−1 M solutions of substrate in MeOH at 25°C under 10 bar hydrogen pressure. S/C denotes molar substrate-to-catalyst ratio. Conversion and enantiomeric excess were determined by chiral GC or chiral HPLC.