A Convenient Synthesis of 2,2′,6,6′-Tetramethoxy-4,4′-bis(dicyclohexylphosphino)-3,3′-bipyridine (Cy-P-Phos): Application in Rh-Catalyzed Asymmetric Hydrogenation of α-(Acylamino)acrylates

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Received: October 11, 2004; Accepted: January 3, 2005

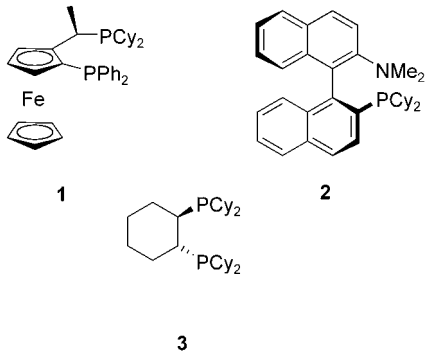
Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: The first example of the synthesis of an axially chiral bis(aryldicyclohexylphosphine) dioxide *via* catalytic hydrogenation of the optically resolved parent bis(aryldiphenylphosphine) dioxide was reported. The procedure for the synthesis of Cy-P-Phos (**4d**) has thus successfully avoided the need for an otherwise lengthy synthetic route owing to the π-excessive nature of one of the aryl groups in the latter. The use of Cy-P-Phos in the Rh(I)-catalyzed asymmetric hydrogenation of the derivatives of methyl (*Z*)-2-acetamidocinnamate gave significantly higher rates of reaction as compared to the use of the previously reported optimal ligand Xyl-P-Phos (**4c**) whilst the level of enantioselectivity was essentially maintained.

Keywords: α-(acylamino)acrylates; asymmetric hydrogenation; dipyridylphosphine; homogeneous catalysis; rhodium

In a transition metal-catalyzed process, the electronic property of the ligand usually plays a crucial role in determining the reactivity of the catalyst. When phosphines are used as ligands, their electronic properties can be tuned by attaching various *P*-substituents (alkyl groups for electron-rich phosphines and aryl groups for comparatively electron-poor phosphines in general). The situation, however, can be confounded when the stereochemical outcome needs to be controlled, particularly so when the non-*P*-chirogenic dialkylphosphino group, often known for its inefficient stereodifferentiability, is required to promote appreciable reactivity. Nevertheless, the fully saturated dicyclohexylphosphine group sometimes displays unique stereo- and electronic control, especially in catalytic asymmetric reactions where the oxidative addition is one of the rate-determining steps. For instance (Scheme 1), Josiphos **1** is industrially employed for the hydrogenation of an imine leading to the synthesis of metolachlor,[1] MAP **2** is efficient in asymmetric Suzuki coupling,[2] vinylation[3] and arylation[4] of ketone enolates, and *trans*-1,2-bis(dicyclohexylphosphino)cyclohexane **3** is utilized in asymmetric hydroboration of styrene derivatives.[5] The dicyclohexylphosphine version in theses cases shows remarkably better performance, in terms of both enantioselectivity and reactivity, as compared to its diphenylphosphine analogues.

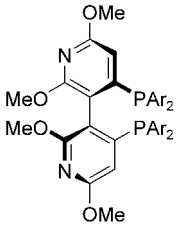
We have recently synthesized a class of atropisomeric dipyridylphosphine ligands, P-Phos (**4a**) and its derivatives **4b – 4c** (Scheme 2)[6] and have established their effectiveness in many catalytic asymmetric hydrogenation reactions[6,7] including the Ru- and Rh-catalyzed asymmetric hydrogenation of methyl esters of a variety of (*Z*)-2-acetamido-3-arylacrylic acids and various β-alkyl-substituted β-(acylamino)acrylates to provide deriv-



1 2 3

Scheme 1. Some chiral ligands containing dicyclohexylphosphine group.

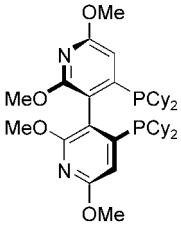
 DOI: 10.1002/adsc.200404310



(*R*)-**4a**, Ar = C_6H_5, (*R*)-P-Phos

(*R*)-**4b**, Ar = 4-$CH_3C_6H_4$, (*R*)-Tol-P-Phos

(*R*)-**4c**, Ar = 3,5-$(CH_3)_2C_6H_3$, (*R*)-Xyl-P-Phos



(*S*)-**4d**, Cy = *c*-C_6H_{11}, (*S*)-Cy-P-Phos

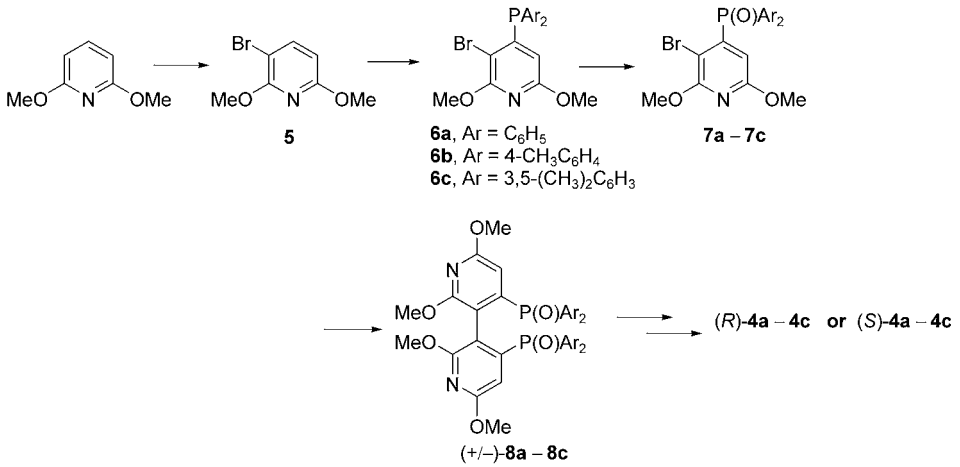
Scheme 2. Chiral dipyridylphosphine ligands **4**.

atives of α- or β-amino acids.[8] In view of the potential usefulness of the dicyclohexylphosphino group as described above, we were interested in probing its efficacy in connection to the six-membered biheteroaryl P-Phos skeleton. This had led us to develop a convenient synthetic route to Cy-P-Phos [**4d**, 2,2′,6,6′-tetramethoxy-4,4′-bis(dicyclohexylphosphino)-3,3′-bipyridine].

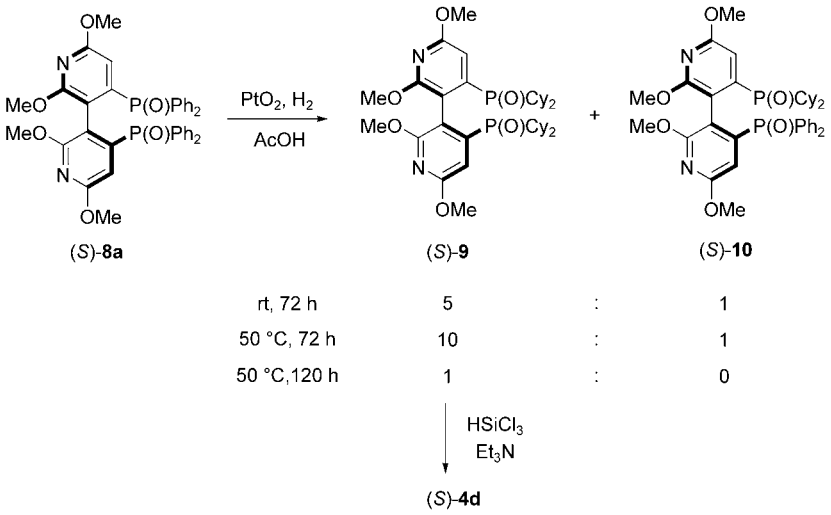
The synthesis of each of the P-Phos members **4a**–**4c** entails the introduction of the phosphinoyl group onto 2,6-dimethoxypyridine before a Cu-mediated Ullmann coupling process to afford the racemic C_2-symmetric diphosphine dioxide **8**. The chiral diphosphine is obtained by optical resolution with enantiopure dibenzoyltartaric acid (DBTA) followed by reduction with trichlorosilane in overall 6 steps as outlined in Scheme 3.[6]

It therefore appeared inevitable at first sight to repeat the above pathway, which encompasses a tedious resolution as in the synthesis of chiral Cy-BICHEP[9] or Cy-BINAP[10] for the synthesis of **4d**. However, capitalizing on the fact that π-excessive aromatic rings are very difficult to hydrogenate, we conjectured that it might be possible to reduce the phenyl groups in **8a** *via* metal-catalyzed hydrogenation whilst leaving the heterocyclic ring intact and giving a bis(aryldialkylphosphine) dioxide. Although the idea of obtaining bis(dicyclohexylphopshine) dioxides *via* hydrogenation of the parent bis(diphenylphosphine) dioxides has been reported, its application has been limited only to the synthesis of bis(alkyldicyclohexylphosphine) dioxides.[11]

In the initial attempt, it was found that the Pd/C system failed to catalyze the hydrogenation of (±)-**8a** to (±)-**9** (Scheme 4) in the mixture of ethanol and acetic acid under 500 psi hydrogen pressure at 50 °C after 36 hours. However, when the catalyst was switched to PtO_2 and the reaction was performed in acetic acid, a mixture of the desired (±)-**9** and partially hydrogenated (±)-**10** (molar ratio = 5:1 according to ^{1}H and ^{31}P NMR analyses) resulted after 72 hours at room temperature (Scheme 4). The ratio of (±)-**9** and (±)-**10** was further improved to 10:1 when the reaction temperature was increased to 50 °C within the same reaction time frame. Finally, pure (±)-**9** was obtained as the exclusive product by simply prolonging the reaction time to 120 hour at 50 °C. Thus, under the same conditions, optically pure **9** was obtained from the hydrogenation of the corresponding enantiomer of **8a**. Single crystals of (*S*)-**9** were obtained by recrystallization in methanol, and the structure of (*S*)-**9** was unambiguously determined by single crystal X-ray diffraction analysis.[12] Reduction of enantiomerically pure **9** with trichlorosilane in the presence of triethylamine in toluene afforded the targeted enantiomer of atropisomeric ligand **4d** in 53% yield. The compound was fully characterized by ^{1}H, ^{13}C, and



Scheme 3. The synthetic route towards **4a**–**4c**.



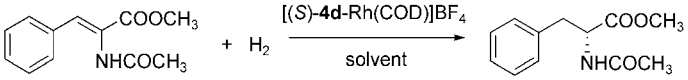
Scheme 4. The synthetic route towards **4d**.

^{31}P NMR spectroscopy, mass spectrometry and elemental analysis.

Next, the rhodium complex [**4d**-Rh(COD)]BF_4 was prepared *in situ* by mixing $Rh(COD)_2BF_4$ with 1.05 equivalents of **4d** in dichloromethane under nitrogen. The ^{31}P NMR spectrum of the resulting complex in $CDCl_3$ exhibited two sets of doublet-of-doublets signals respectively centered at $\delta = 12.7$ ($J_{Rh,P} = 145$ Hz, $J_{P,P} = 23.7$ Hz) and 24.3 ($J_{Rh,P} = 124.0$ Hz, $J_{P,P} = 23.7$ Hz). This is somehow intriguing as the intuitively C_2-symmetric complex turned out to be non-symmetric in solution and is in sharp contrast to the analogous Rh(I) complexes formed from the other members of the P-Phos family.[8] This observation was consistent with a reported X-ray crystal structure of [Rh(*S*-Cy-BINAP)(COD)]-ClO_4, which differed distinctly from similar Rh complexes derived from C_2-symmetric bisphosphines bearing four *P*-phenyl rings, in that it did not approximate to C_2-symmetry.[10] The four cyclohexyl groups appear to be disposed in an edge-face-face-face arrangement rather than in an edge-face-edge-face orientation and the seven-membered chelate ring was remarkably distorted from a δ-skew conformation. The non-equivalence of the two phosphorus atoms in [Rh(*S*-Cy-BINAP)(COD)]ClO_4 was also reflected in the distinctly variable Rh-P distances [2.331(2) and 2.422(2) Å for P(1) and P(2), respectively] and in the ^{31}P NMR spectrum [$\delta = 12.1$ (dd, $J_{Rh,P} = 145.7$ Hz, $J_{P,P} = 19.9$ Hz) and 31.1 (dd, $J_{Rh,P} = 125.2$ Hz, $J_{P,P} = 19.9$ Hz)].[10]

For the evaluation of the effectiveness of **4d**, we selected one of the most popular test reactions – the rhodium-catalyzed enantioselective hydrogenation of methyl (*Z*)-2-acetamidocinnamates. High enantioselectivity was achieved (up to 98% ee) by the employment of Cy-BICHEP as chiral ligand in the rhodium-catalyzed enantioselective hydrogenation of ethyl (*Z*)-2-acetamidocinnamates.[9] Our previous work indicated that

Table 1. The effects of solvent, hydrogen pressure and reaction temperature on the hydrogenation of methyl (*Z*)-2-acetamidocinnamate (**11**) catalyzed by [(*S*)-**4d**-Rh(COD)]BF_4.[a]



11 (*R*)-**12**

Entry	Solvent	H_2 [atm]	*T* [°C]	ee [%][b]
1	Methanol	1	rt	90 (90)[c]
2[d]	Methanol	1	0	93 (94)[c]
3	THF	1	rt	89
4	CH_2Cl_2	1	rt	78
5	Toluene	1	rt	94
6	Acetone	1	rt	95
7	Acetone	15	rt	87
8	Acetone	35	rt	86
9[d]	Acetone	1	0	97

[a] Reaction conditions: 2 hours; 4.4 mg substrate; substrate concentration = 0.09 M; substrate/catalyst = 100 (M/M), 100% conversion was observed in all cases.

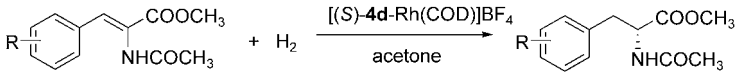
[b] The conversions and ee values were determined by chiral GC with a 25 m × 0.25 mm Chrompack Chirasil-*L*-Val column.[13] The *R* configuration was obtained for all products. The absolute configuration was determined by comparing the retention time with that reported in the literature (Ref.[13]).

[c] The value in parenthesis represents the enantioselectivity achieved by [**4c**-Rh(COD)]BF_4 under otherwise identical conditions.[8a]

[d] Reaction time = 8 h.

methanol was the preferred solvent for Rh-catalyzed hydrogenation of methyl esters of a variety of (*Z*)-2-acetamido-3-arylacrylic acids when using **4a**–**4c** as chiral ligands.[8a] Under the preferred conditions in the use of **4a**–**4c**, **4d** possessed similar enantioselectivity (90%

Table 2. Asymmetric hydrogenation of the derivatives of methyl (*Z*)-2-acetamidocinnamate catalyzed by [(*S*)-**4d**-Rh(COD)]BF_4.[a]



Entry	Substrate, R=	Time [h]	*T* [°C]	ee [%][b]
1	H	8	0	97
2	2-Cl	2	rt	87
3	2-Cl	8	0	90
4	3-Cl	2	rt	91
5	3-Cl-	8	0	92
6	4-Cl	2	rt	89
7	4-Cl	8	0	91
8	4-CH_3	8	0	93
9	4-CH_3O	8	0	95

[a] Reaction conditions: 4 mg substrate; 1 atm hydrogen pressure; substrate concentration = 0.075 M in acetone; substrate/catalyst = 100 (M/M), 100% conversion was observed in all cases.

[b] The conversions and ee values were determined by NMR and chiral GC with a 25 m × 0.25 mm Chrompack Chirasil-*L*-Val column.[13] The *R* configuration was obtained for all products. The absolute configuration was determined by comparing the retention time with that reported in the literature (Ref.[13]).

ee, Table 1, entry 1) with the optimal ligand **4c** for the asymmetric hydrogenation of methyl (*Z*)-2-acetamidocinnamate (**11**). When the experiment was performed at 0 °C, the rate of hydrogenation effected by [**4d**-Rh(COD)]BF_4 (8 h, entry 2) was accelerated over twofold when compared with the analogous Rh(I) complexes derived from **4c** under otherwise identical conditions (18 h)[8a] whilst the level of enantioselectivity was essentially maintained, indicative of the beneficial effect of the electron-rich dicyclohexylphosphino moiety. Furthermore, by carrying out the reaction in a variety of common organic solvents, we found that acetone was the most preferable solvent for the enantioselective hydrogenation of **11** catalyzed by [**4d**-Rh(COD)]BF_4 (Table 1, entry 6 *vs.* entries 1 and 3–5). As with many other ligands investigated in this reaction, the use of a low hydrogen pressure was conducive to selectivity (Table 1, entries 7 and 8 *vs.* entry 6). Also, the reaction was best performed at a lower temperature for achieving excellent selectivity (entry 9 *vs.* entry 5).

Further studies of the hydrogenation of other prochiral acetamidoacrylic esters confirmed that the enantioselectivity of [**4d**-Rh(COD)]BF_4 was quite consistent. A variety of derivatives of methyl (*Z*)-2-acetamidocinnamate were hydrogenated with this catalyst and in most cases the desired products were found to have ee values of $\geq$ 90%. More detailed data are summarized in Table 2. It was found that the presence of electron-donating groups on the phenyl group of methyl (*Z*)-2-acetamidocinnamate led to slightly more favorable ees than electron-withdrawing groups (entries 8 and 9 *vs.* entries 3, 5 and 7).

In summary, we have reported the first example of the synthesis of an axially chiral bis(aryldicyclohexylphosphine) **4d** *via* the catalytic hydrogenation of the enantiomerically pure parent bis(aryldiphenylphosphine) dioxide **8a**. Because of the π-excessive nature of one of the aryl groups in the latter, this procedure has successfully avoided the need for an otherwise lengthy synthetic route. The use of **4d** in the Rh(I)-catalyzed asymmetric hydrogenation of the derivatives of methyl (*Z*)-2-acetamidocinnamate showed substantially higher reaction rates as compared to that obtained using previously reported optimal ligand **4c** whilst the level of enantioselectivity was essentially maintained. Further work is currently in progress aiming at broadening the application of this ligand in other asymmetric reactions.

Experimental Section

Preparation of the Stock Solution of [(*S*)-4d-Rh(COD)]BF_4

(*S*)-Cy-P-Phos [(*S*)-**4d**, 7.0 mg, 10.5 μmol] was dissolved in CH_2Cl_2 (0.5 mL) under nitrogen. A solution of $[Rh(COD)_2]BF_4$ (4.1 mg, 10.0 μmol) in CH_2Cl_2 (0.5 mL) was added dropwise to the above solution with stirring. The reaction mixture was stirred overnight to give a solution of [(*S*)-**4d**-Rh(COD)]BF_4 (0.01 mol·L^{-1}). ^{31}P NMR ($CDCl_3$, 202 MHz): δ = 12.7 ($J_{Rh,P}$ = 145 Hz, $J_{P,P}$ = 23.7 Hz), 24.3 ($J_{Rh,P}$ = 124.0 Hz, $J_{P,P}$ = 23.7 Hz.

Procedures for the Synthesis of (*S*)-4d

See Supporting Information.

Typical Procedure for the Asymmetric Hydrogenation of Methyl (*Z*)-2-Acetamidocinnamate

A solution of 0.01 mol·L^{-1} [(*S*)-**4d**-Rh(COD)]BF_4 in CH_2Cl_2 (20 μL, 2×10^{-4} mmol), methyl (*Z*)-2-acetamidocinnamate (4.37 g, 0.02 mmol) and acetone (200 μL) were charged to a 25-mL round-bottom flask equipped with a magnetic stirring bar under a nitrogen atmosphere. A stream of H_2 was bubbled through the solution while it was magnetically stirred at ambient temperature for 2 h. The conversion and the enantiomeric excess of the product (*R*)-2-acetamido-3-phenylpropanoate [(*R*)-**12**] were determined by NMR and chiral GC analysis to be > 99.9% and 95%, respectively (column, Chrompack Chirasil-*L*-Val, 25 m × 0.25 mm, carrier gas, N_2).[13]

Acknowledgements

We thank the University Grants Committee Area of Excellence Scheme in Hong Kong (AoE P/10–01) and The Hong Kong Polytechnic University ASD Fund for financial support of this study.

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