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# 3,3′-Disubstituted BINAP Ligands: Synthesis, Resolution, and Applications in Asymmetric Hydrogenation

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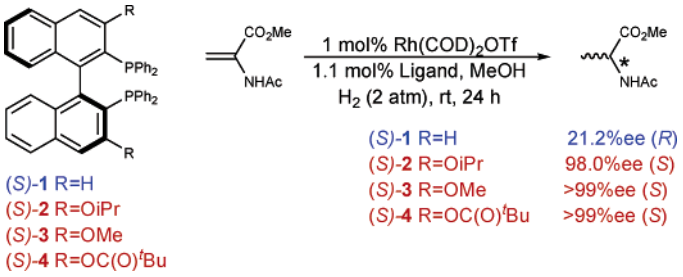
## ABSTRACT




**A novel family of BINAP ligands were prepared with alkoxy- and acetoxy-derived substituents in the 3,3′-positions. They were prepared through a convergent synthesis starting from readily available 4-bromo-2-naphthol. These ligands afforded excellent enantioselectivities in the asymmetric hydrogenation of substituted olefins. The presence of the 3,3′-substituents was shown to be beneficial by a direct comparison with the parent unsubstituted BINAP.**

Catalytic asymmetric synthesis is one of the most powerful methods for the construction of an array of enantiomerically enriched compounds. The field of ligand design, specifically the design of new chiral bisphosphine ligands, is crucial for the further development of highly efficient transition metal-catalyzed processes. Despite the fact that a diverse array of phosphine ligands are known, continued entries into this class are of great importance. We report here a convergent approach to a novel class of substituted BINAP ligands (**2**−**5**), containing substitution at the 3,3′-positions. Greatly enhanced levels of enantioselectivity in the asymmetric hydrogenation of substituted olefins over that of unsubstituted BINAP (**1**) illustrate the potential benefits of this extra substitution.

The biaryl family of bisphosphine ligands, pioneered by BINAP (**1**, Figure 1),[1] have proven to be excellent ligands for many transition metal-catalyzed asymmetric reactions.[2] Given the fact that BINAP is not a superior ligand for all of

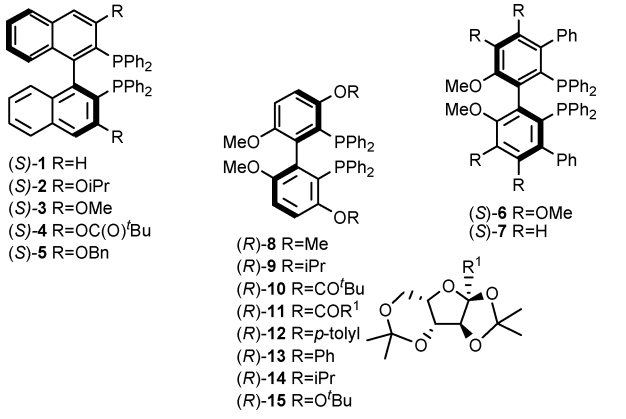



**Figure 1.** 3,3′-Disubstituted biaryl bisphosphine ligands.

(1) (a) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 2000. (c) Noyori, R. *Asymmetric Catalysis In Organic Synthesis*; Wiley: New York, 1994.

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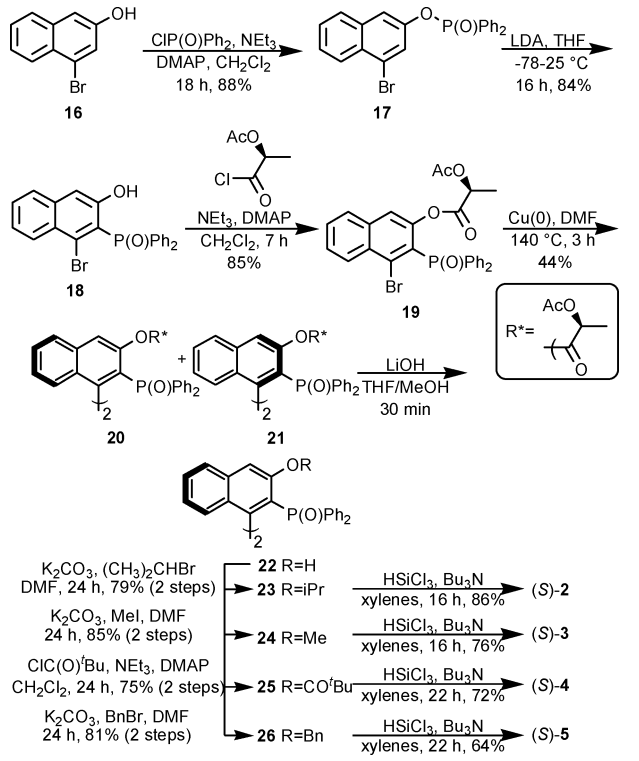
these processes, it is obvious that varied electronic and structural properties of new ligands can lead to greater selectivity. We envisioned using the successful biaryl framework and incorporating structural variations at a position close to the site of metal coordination, the 3,3′-positions, as an entry into a new class of ligands. In a recent review of modified BINAP ligands, Lemaire states that the 3 and 3′ are the positions for which introduction of further substitution could most influence the electronic density of the phosphorus donor and the steric environment around the catalytic site.[3] Looking at the positive results that have been obtained in many cases with 3,3′-disubstituted BINOL ligands,[4,5] and given the fact that this substitution pattern is absent from current modified BINAP ligands,[6,7] it was felt that an approach to this class would be beneficial. Previous disclosures of 3,3′-disubstituted biaryl bisphosphine ligands have been made for the analogous biphenyl class of ligands. Zhang's *o*-Ph-hexaMeO−BIPHEP[8] (**6**) and *o*-Ph-MeO−BIPHEP[9] (**7**) have proven to be successful in the asymmetric hydrogenation of cyclic enamides and dehydroamino acids. Results from our lab using BIPHEP derivatives **8**−**15** have proven to be successful catalysts in asymmetric Heck and hydrogenation reactions.[10]

Our synthesis began from readily available 4-bromo-2-naphthol (**16**),[11] which was treated with diphenylphosphinic chloride in the presence of triethylamine and DMAP to afford phosphinate **17** (Scheme 1). Regioselective migration of the diphenylphosphinyl unit upon treatment of **17** with LDA afforded phosphine oxide **18**.[12] The existence of a free OH group proved to be important, as it provided an attachment point for a chiral auxiliary, which upon Ullmann coupling, would facilitate the formation of diastereomers for separation of the generated axial isomers. Reaction of **18** with (+)-lactic acid-derived (*S*)-2-acetoxypropanoyl chloride[13] afforded **19**, which underwent subsequent Ullmann coupling to generate a mixture of diastereomers **20** and **21**. The coupling proceeded with a moderate diastereoselectivity (≈2:1 by $^{31}$P NMR), and the major diastereomer could be isolated readily by column chromatography[14] and trituration with *tert*-butylmethyl ether. Facile saponification of the chiral auxiliary afforded optically pure (*S*)-3,3′-(OH)$_2$−BINAP(O) **22**, which could readily be converted into a variety of substrates. The phosphine oxides **23**−**26** were formed by standard methods, which after reduction with trichlorosilane yielded phosphines **2**−**5**. The absolute stereochemistry of the axis of chirality for the major diastereomer from the Ullmann coupling was determined to be $S_{ax}$ from the X-ray crystal structure of the phosphine selenide derived from (*S*)-**2** upon crystallization from EtOAc/hexanes (Figure 2).[15]

**Scheme 1.** Synthesis of 3,3′-Disubstituted BINAP Derivatives




To better understand the effects of the 3,3′-substituents on metal coordination, the newly synthesized ligands were reacted with a stoichiometric amount of $(PhCN)_2PdCl_2$ to generate the corresponding palladium dichloride adducts (see Table 1). X-ray crystal structure analysis[16] of (*S*)-**27** and (*S*)-**28** (Supporting Information) allowed for a direct comparison with the known BINAP structure.[17] It was observed that the average Pd−P and Pd−Cl bonds remained fairly constant for all of the ligands and that the chiral pocket found in the

(2) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(3) (a) Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, *105*, 1801. (b) For a recent review on biaryl bisphosphine ligands, see: Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *105*, 857.

(4) (a) Chen, Y.; Yekta, S.; Yudin, A. *Chem. Rev.* **2003**, *103*, 3155. (b) Kocovsky, P.; Vyskocyl, S.; Smrcina, M. *Chem. Rev.* **2003**, *103*, 3213. (c) Pu, L. *Chem. Rev.* **1998**, *98*, 2405.

(5) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857.

(6) For a 4,4′-disubstituted BINAP, see: Ngo, H. L.; Lin, W. *J. Org. Chem.* **2005**, *70*, 1177. For a 5,5′-derivative, see: Deng, G.; Fan, Q.; Chen, X.; Liu, D.; Chan, A. S. *Chem. Commun.* **2002**, 1570. For a 6,6′-derivative, see: Ngo, H. L.; Hu, A.; Lin, W. *Chem. Commun.* **2003**, 1912. For a 7,7′-derivative, see: Che, D.; Andersen, N. G.; Lau, S. Y. W.; Parvez, M.; Keay, B. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1919.

(7) To the best of our knowledge, no report of the synthesis, characterization or applications of any 3,3′-disubstituted BINAP ligands have been reported to date. While the Lemaire review of ref 3 cites a patent that outlines a synthetic proposal for such ligands, no experimental detalis were provided. Zhang, X. (The Penn State Research Foundation). PCT. Int. Appl. WO 02/40491, 2002.

(8) Tang, W.; Chi, Y.; Zhang, X. *Org. Lett.* **2002**, *4*, 1695.

(9) Wu, S.; He, M.; Zhang, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2177.

(10) (a) Gorobets, E.; Sun, G.; Wheatley, B. M. M.; Parvez, M.; Keay, B. A. *Tetrahedron Lett.* **2004**, *45*, 3597. (b) Gorobets, E.; Wheatley, B. M. M.; Hopkins, J. M.; McDonald, R.; Keay, B. A. *Tetrahedron Lett.* **2005**, *46*, 3843.

(11) Newman, M. S.; Sankaran, V.; Olson, D. R. *J. Am. Chem. Soc.* **1976**, *98*, 3237.

(12) This regioselective migration has been observed previously for the nonbrominated npahthalene; see: Dhawan, B.; Redmore, D. J. *J. Org. Chem.* **1991**, *56*, 833.

(13) Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **1999**, *55*, 2431.

(14) $R_f$ of **16** = 0.29, $R_f$ of **17** = 0.18 (5% MeOH/$CHCl_3$).

(15) Crystal data for the phosphine selenide of ($S_{ax}$)-**2**: orthorhombic $P2_12_12_1$; $a$ = 11.4539(12) Å, $b$ = 15.6457(17) Å, $c$ = 23.672(7) Å, α = 90°, $\beta$ = 90°, $\gamma$ = 90°, $V$ = 4242.1(14) Å$^3$; $Z$ = 4; $R$ = 0.032; $R_w$ = 0.066. The absolute structure was determined by the Flack method (Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876). The Flack parameter for the inverted structure was 1.003(6). Therefore, the inverted structure was rejected as the one present in the crystal.

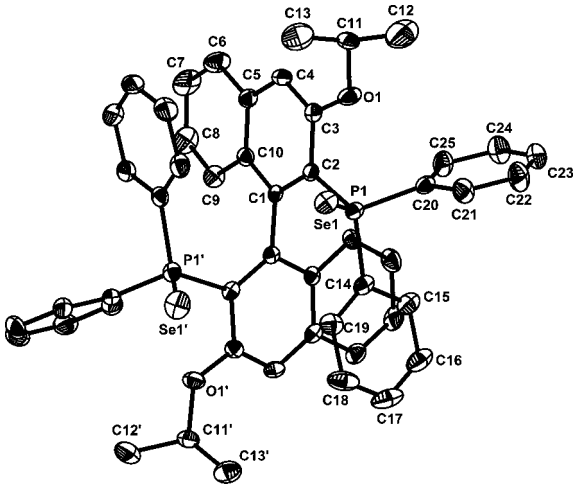
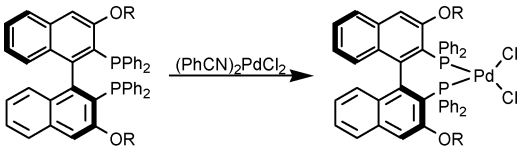



**Figure 2.** X-ray crystal structure of the phosphine selenide of (*S*)-**2**.

**Table 1.** Structural Parameters for $PdCl_2$ Complexes of (*S*)-**1**−**3**




(*S*)-**2** R=iPr
(*S*)-**3** R=Me

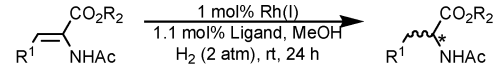
(*S*)-**27** R=iPr
(*S*)-**28** R=Me

| entry | 3,3′-substituent | average Pd−P (Å) | average Pd−Cl (Å) | ligand bite angle (deg) | torsion angle (deg) |
|---|---|---|---|---|---|
| 1 | H | 2.245 | 2.350 | 92.77 | 68.42 |
| 2 | OiPr | 2.290 | 2.338 | 89.91 | 62.64 |
| 3 | OMe | 2.270 | 2.355 | 88.09 | 60.25 |

BINAP structure, with one of the phenyl substituents on each of the phosphorus atoms undergoing a $\pi$-stacking interaction with the binaphthalene backbone, was maintained upon introduction of the 3,3′-substituents. The ligand bite angles (∠P−Pd−P) were compared, and for both the complexes, a tightening of this angle was observed compared to BINAP. Directly related to this is the torsion angle (∠C2−C1−C1′−C2′) formed by the twisting of the binaphthalene backbone. A decrease in this angle was again observed for the 3,3′-complexes. These structural data suggest that a rigid chiral pocket still remains upon incorporation of groups in the 3,3′-positions of BINAP but that significant steric constraints have been placed upon the metal, which will most certainly alter substrate binding for further transformation.

Ligands (*S*)-**2**−**5** were used in the hydrogenation of substituted olefins, and the results were compared directly to those with unsubstituted BINAP (**1**) under identical reaction conditions. Table 2 contains results for the hydrogenation of acrylic and cinnamic acid derivatives. The catalyst was prepared in situ by stirring a solution of the Rh precursor and the phosphine ligand prior to introduction of the olefin and being pressurized under $H_2$. These new ligands proved to be very selective for the hydrogenation of the acrylate derivatives when compared to BINAP. Very low levels of enantioselectivity were observed for BINAP (entries 1 and 2), whereas introduction of groups in the 3,3′-positions led to dramatic increases in selectivity. Of the four derivatives, the OBn analogue (*S*)-**5** gave the lowest selectivity of the three (entries 13 and 14), while the OMe and OCO*t*Bu derivatives produced nearly enantiopure products (entries 7, 8, 10, and 11). It is interesting to note that the 3,3′-disubstituted ligands provided the product of the opposite configuration to that of BINAP, despite the fact that all of the ligands were of the $S_{ax}$ configuration. When a more hindered olefin was subjected to similar reduction conditions (Table 2, $R^1$ = Ph), the enantioselectivity levels were still greater than that of BINAP (entry 3 vs entries 6, 9, 12, and 15) but were much lower compared to the results obtained with the disubstituted olefin. The OCO*t*Bu ligand (*S*)-**4** provided the best results with 74.7% ee, and as was observed

**Table 2.** Asymmetric Hydrogenation of 2-Acetamidoacrylic Acid Derivatives with Ligands (*S*)-**1**−**5**




**29** $R^1$=H, $R^2$=H
**30** $R^1$=H, $R^2$=Me
**31** $R^1$=Ph, $R^2$=Me

**32** $R^1$=H, $R^2$=H
**33** $R^1$=H, $R^2$=Me
**34** $R^1$=Ph, $R^2$=Me

| entry[a] | ligand | olefin | ee (%)[b] |
|---|---|---|---|
| 1 | (*S*)-**1** | 29[c] | 33.8 (*R*) |
| 2 | | 30 | 21.2 (*R*) |
| 3 | | 31 | 14.8 (*R*) |
| 4 | (*S*)-**2** | 29[c] | 94.9 (*S*) |
| 5 | | 30 | 98.0 (*S*) |
| 6 | | 31 | 23.2 (*S*) |
| 7 | (*S*)-**3** | 29[c] | 98.6 (*S*) |
| 8 | | 30 | >99 (*S*) |
| 9 | | 31 | 32.8 (*S*) |
| 10 | (*S*)-**4** | 29[c] | >99 (*S*) |
| 11 | | 30 | >99 (*S*) |
| 12 | | 31 | 74.7 (*S*) |
| 13 | (*S*)-**5** | 29[c] | 92.3 (*S*) |
| 14 | | 30 | 96.3 (*S*) |
| 15 | | 31 | 44.8 (*S*) |

[a] All reactions proceeded with complete conversion. Reactions of olefins **29** and **30** used $Rh(COD)_2OTf$ as the Rh source. Reactions of olefin **31** used $Rh(NBD)_2BF_4$ as the Rh source. [b] For **33**, determined by chiral GC on a Cyclodex B column; for **34**, determined by chiral HPLC on a Chiralcel OD column. [c] Ee determined upon conversion to the methyl ester.

(16) Crystal data for (*S*)-**27**: orthorhombic $P2_12_12_1$; $a$ = 14.653(2) Å, $b$ = 17.076(2) Å, $c$ = 18.442(2) Å, α = 90°, $\beta$ = 90°, $\gamma$ = 90°, $V$ = 4614.5(10) Å$^3$, $Z$ = 4, $R$ = 0.040; $R_w$ = 0.085. Crystal data for (*S*)-**28**: triclinic $P1$; $a$ = 12.359 (5) Å, $b$ = 12.929(5) Å, $c$ = 14.434 (5) Å, α = 76.435(5)°, $\beta$ = 69.693(5)°, $\gamma$ = 74.968(5)°, $V$ = 2062.3(14) Å$^3$, $Z$ = 2, $R$ = 0.0399; $R_w$ = 0.1120.

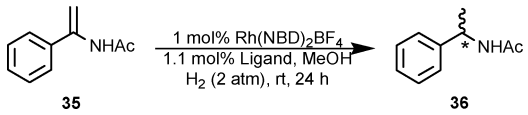
(17) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K. *Organometallics* **1993**, *12*, 4188.

for the less hindered olefin, the ligands with 3,3′-substituents afforded the product with the opposite stereochemistry to that of BINAP of the same axial configuration.

The asymmetric hydrogenation of enamides is another reaction often used to probe the efficacy of new bisphosphine ligands. Table 3 contains results for the hydrogenation of a simple enamide. The catalyst was again prepared in situ, and while the results obtained with this substrate did not provide levels of induction as high as those in Table 2, significant improvements over BINAP were observed for ligands (*S*)-**2** and (*S*)-**4**. It was again observed that the opposite product enantiomer was formed for the 3,3′-disubstituted ligands versus that with BINAP, despite the fact that all of the ligands were of the $S_{ax}$ configuration. These results further suggest that the incorporation of groups ortho to the phosphine substituents can have a beneficial effect on enantioselectivity for processes in which the lack of substitution provides low levels of enantioselectivity.

As these early results indicate, substituents at the 3,3′-positions of BINAP can indeed have a beneficial effect on enantioselectivity when compared to the unsubstituted ligand. This additional substitution leads to a different coordination environment around the metal center upon ligation, leading to enhanced asymmetric induction. The well studied mechanism of hydrogenation for these types of olefins involves the formation of two diastereomeric Rh−olefin complexes.[18] It was shown that the minor diastereomeric complex of this mixture actually leads to the observed major product. Given the reversal of stereochemistry observed with our ligands, it appears that the introduction of 3,3′-substituents alters the equilibrium mixture of the two diastereomeric olefin complexes, allowing the major one to react with $H_2$ and lead to the product with the opposite stereochemistry. Further studies to probe this mechanism are currently under way.

**Table 3.** Asymmetric Hydrogenation of *N*-Acetyl-phenylethenamide with Ligands (*S*)-**1**−**5**




**35** **36**

| entry[a] | ligand | ee (%)[b] |
|---|---|---|
| 1 | (*S*)-**1** | 10.7 (*R*) |
| 2 | (*S*)-**2** | 89.9 (*S*) |
| 3 | (*S*)-**3** | 26.9 (*S*) |
| 4 | (*S*)-**4** | 85.6 (*S*) |
| 5 | (*S*)-**5** | 59.6 (*S*) |

[a] All reactions proceeded with complete conversion. [b] Determined by chiral GC using a Cyclodex B column.

In summary, we have devised a short, convergent synthesis to this novel class of phosphine ligands and have demonstrated their potential for improvement in processes in which BINAP itself gives poor results. We are continuing to pursue the synthesis of further derivatives of this class with new 3,3′-substituents and expanding the scope of their applications as well as investigating the cause for the reversal in absolute configuration of the hydrogenation products. These results will be reported in due time.

**Acknowledgment.** Financial support for this work was porvided by Merck Frosst Canada and by the Natural Sciences and Engineering Research Council of Canada through a CRD grant to B.A.K. and an NSERC postgraduate scholarship to J.M.H. The Alberta Ingenuity Fund is also thanked for a studentship to J.M.H. Thanks are extended to S.A.D. and M.P. for crystal structure determination.

**Supporting Information Available:** Full experimental procedure for the synthesis of ligands **2**−**5**, along with spectral data, and a general procedure for the hydrogenation of substituted olefins and chiral GC data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051413D

(18) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746.