

# A Novel Class of Nonbiaryl Atropisomeric P,O-Ligands for Palladium-Catalyzed Asymmetric Allylic Alkylation<sup>†</sup>

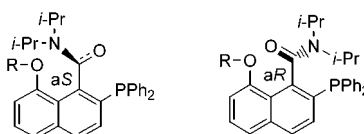
Wei-Min Dai,\* Kelly Ka Yim Yeung, Jin-Teng Liu, Ye Zhang, and Ian D. Williams

Department of Chemistry and Open Laboratory of Chirotechnology of The Institute of Molecular Technology for Drug Discovery and Synthesis, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

chdai@ust.hk

Received March 5, 2002

## ABSTRACT



R = H, Me, PhCH<sub>2</sub>, (1S)-(-)-camphanic

A novel class of nonbiaryl atropisomeric P,O-ligands possessing an *N,N*-dialkyl-1-naphthamide skeleton has been synthesized via an efficient chemical resolution process. It represents the first example of axially chiral P,O-ligands devoid of central chirality. Up to 94.7% ee was obtained for the Pd-catalyzed asymmetric allylic alkylation (AAA). Effects of solvent, base, and the bulk of the C8 oxygen group of the P,O-ligand on the AAA reaction were examined.

Catalytic asymmetric synthesis is commonly achieved through organometallic chemistry of transition metals by employing chiral ligands, in particular, the phosphorus based ligands.<sup>1</sup> Bidentate chiral ligands enjoy wide application in both academic research and industrial processes because they form relatively rigid metal complexes and afford better stereo-differentiation in catalysis. For instance, C<sub>2</sub> symmetric chiral

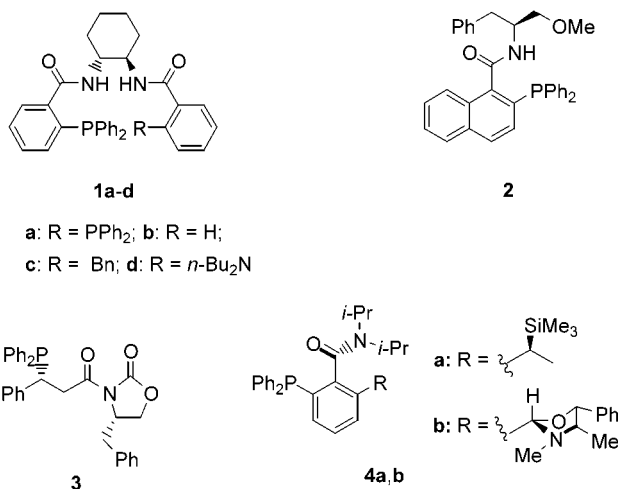
diphosphines (P,P-ligands) have been widely used in asymmetric hydrogenation and other catalytic reactions as represented by (*R*)- or (*S*)-BINAP and Trost's diphosphine **1a** (Figure 1).<sup>2</sup> The latter is one of the most successful chiral P,P-ligand systems for asymmetric allylic alkylation (AAA) based on the "chiral pocket" concept.<sup>2c,d,f</sup> Non-C<sub>2</sub> symmetric chiral bidentate ligands, including chiral P,N<sup>3</sup> and dinitrogen<sup>2f,4</sup>

<sup>†</sup> The Institute of Molecular Technology for Drug Discovery and Synthesis is supported by The Areas of Excellence Scheme (AoE/P-10/01) established under The University Grants Committee of Hong Kong SAR, China.

(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) *Catalytic Asymmetric Synthesis*, 2nd ed; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

(2) For recent reviews, see: (a) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, 3, 1089. (b) Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; pp 325–365. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, 96, 395. (d) Trost, B. M. *Acc. Chem. Res.* **1996**, 29, 355. (e) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, pp 833–884. (f) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 593–649.

(3) For selected examples, see: (a) Matt, P. v.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 566. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, 34, 1769. (c) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, 34, 3149. (d) Kubota, H.; Koga, K. *Tetrahedron Lett.* **1994**, 35, 6689. (e) Schnyder, A.; Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 931. (f) Mino, T.; Imiya, W.; Yamashita, M. *Synlett* **1997**, 583. (g) Pretot, R.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 323. (h) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 2897. (i) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 3047. (j) Vyskočil, S.; Smrtna, M.; Hanu, V.; Poláček, M.; Koovsk, P. J. *Org. Chem.* **1998**, 63, 7738. (k) Gilbertson, S. R.; Chang, C.-W. T. *J. Org. Chem.* **1998**, 63, 8424. (l) Cahill, J. P.; Guiry, P. J. *Tetrahedron: Asymmetry* **1998**, 9, 4301. (m) Stranne, R.; Vasse, J.-L.; Moberg, C. *Org. Lett.* **2001**, 3, 2525. (n) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, 123, 7471. Also see: (o) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, 33, 336.

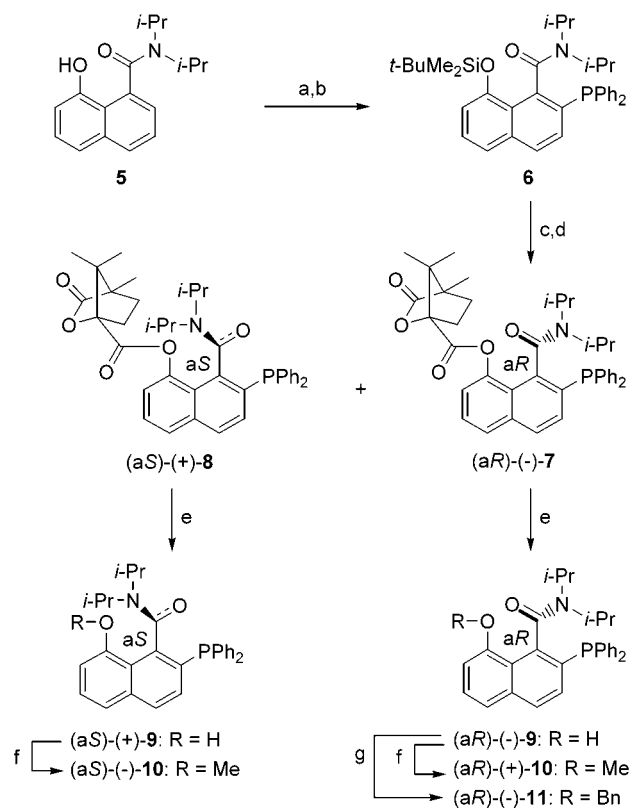


**Figure 1.** Structures of known P,P- and P,O-ligands for AAA.

ligands, give excellent regioselectivity and enantioselectivity in AAA. The diphosphine **1a** can form a P,O-chelate with palladium as well.<sup>5</sup> One such complex, being catalytically active, was confirmed by X-ray crystallographic analysis.<sup>5b</sup> Non-C<sub>2</sub> symmetric ligands **1b,c** were reported to give low and reversed ee's in AAA compared to that of **1a**.<sup>5a</sup> Interestingly, ligand **1d** competes between P,O- and P,N-chelation with palladium and gives up to ca. 80% ee's in AAA.<sup>5c</sup> Very recently, the amide-based P,O-ligands **2–4** were reported to give 74–90% ee's in AAA.<sup>6</sup> Notably, ligands **4a,b** possess both central and axial chiralities; however, the amide moiety in **2** seems conformationally labile and unlikely to contribute to asymmetric induction. We report here a novel class of nonbiaryl atropisomeric<sup>7</sup> P,O-ligands **9–11** devoid of central chirality and demonstrate their application in AAA.<sup>8</sup>

Our synthesis started with the known 1-naphthamide **5**<sup>9</sup> as shown in Scheme 1. Protection of the 8-hydroxyl group in **5** afforded the TBDMS ether. The latter was metalated at the C2 position, directed by the amide moiety,<sup>10</sup> followed by reacting with PPh<sub>2</sub>Cl to afford racemic **6**. Removal of the silyl group in **6** and reaction of the resultant 8-naphthol

**Scheme 1.** Synthesis of Nonbiaryl Atropisomeric P,O-Ligands<sup>a</sup>



<sup>a</sup> (a) *t*-BuMe<sub>2</sub>SiCl, imidazole, DMF, 45 °C, 20 h (96%); (b) *s*-BuLi, THF, –78 °C, 1 h; then Ph<sub>2</sub>PCL, –78 °C, 4 h (87%); (c) TBAF, THF, rt, 40 min (95%); (d) (1*S*)-(-)-camphanic chloride, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 12 h (**7**, 49% and **8**, 48%); (e) 10% KOH, THF, rt, 4 h (80%); (f) NaH, MeI, THF, rt, 4 h (91%); (g) NaH, BnBr, THF, rt, 24 h (61%).

with (1*S*)-(-)-camphanic chloride (DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt) furnished the diastereomers (a*R*)-(-)-**7** and (a*S*)-(+)-**8**, which were separated by flash column chromatography over silica gel. Attempts to grow single crystals of (a*S*)-(+)-**8** in CH<sub>2</sub>Cl<sub>2</sub>–hexane at 5–10 °C for a week resulted in hydrolysis of the ester to give single crystals of both the alcohol (a*S*)-(+)-**9** and (1*S*)-(-)-camphanic acid. Alkaline saponification of (a*R*)-(-)-**7** and (a*S*)-(+)-**8** gave (a*R*)-(-)-**9** and (a*S*)-(+)-**9**, respectively, which were methylated to afford the P,O-ligands (a*R*)-(+)-**10** and (a*S*)-(-)-**10**. Similarly, benzylation of (a*R*)-(-)-**9** gave (a*R*)-(-)-**11**. The absolute stereochemistry of (a*S*)-(+)-**9** and (a*R*)-(+)-**10** was determined by X-ray crystallographic analysis (Figure 2, also see Supporting Information). It should be emphasized that the chiral axes in **7–11** are quite stable at ambient temperature due to an electronic effect of the C8 oxygen with the amide carbonyl group.<sup>11</sup> In fact, no racemization was detected after refluxing (a*R*)-(+)-**10** in toluene for 10 h.

We evaluated **7**, **8**, **10**, and **11** in the AAA of 1,3-diphenylprop-2-enyl acetate **12**. The results are summarized in Table 1. With 1:1.4 ratio of Pd:ligand, the reaction

(4) For a recent review on nitrogen-containing ligands, see: Fache, F.; Schulz, E.; Tommasino, M. L.; Léniaire, M. *Chem. Rev.* **2000**, *100*, 2159.

(5) (a) Trost, B. M.; Breit, B.; Organ, M. G. *Tetrahedron Lett.* **1994**, *35*, 5817. (b) Butts, C. P.; Crosby, J.; Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Commun.* **1999**, 1707. (c) Kim, Y. K.; Lee, S. J.; Ahn, K. H. *J. Org. Chem.* **2000**, *65*, 7807.

(6) (a) Clayden, J.; Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem.* **2000**, *65*, 7033. (b) Clayden, J.; Lai, L. W.; Helliwell, M. *Tetrahedron: Asymmetry* **2001**, *12*, 695. (c) Mino, T.; Kashihara, K.; Yamashita, M. *Tetrahedron: Asymmetry* **2001**, *12*, 287. (d) Gilbertson, S. R.; Lan, P. *Org. Lett.* **2001**, *3*, 2237. Also see: Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Eur. J.* **1998**, *4*, 2539.

(7) Clayden, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 949.

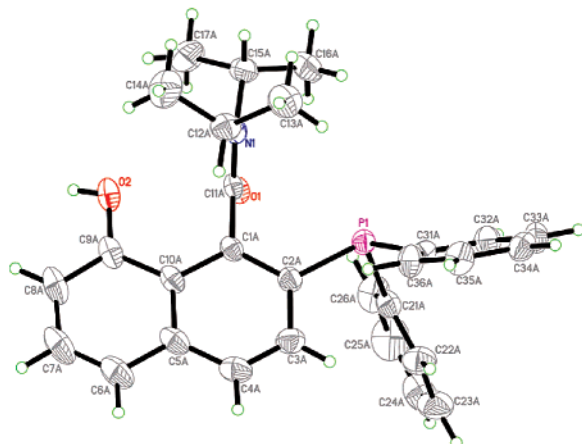
(8) Preliminary results were reported at The 2nd National Symposium on Organic Chemistry in conjunction with The 1st National Symposium on Chemical Biology, Hangzhou, China, November 1–4, 2001, p 108 and Singapore International Chemical Conference-2, Singapore, December 18–20, 2001, p 42.

(9) Clayden, J.; Frampton, C. S.; McCarthy, C.; Westlund, N. *Tetrahedron* **1999**, *55*, 14161.

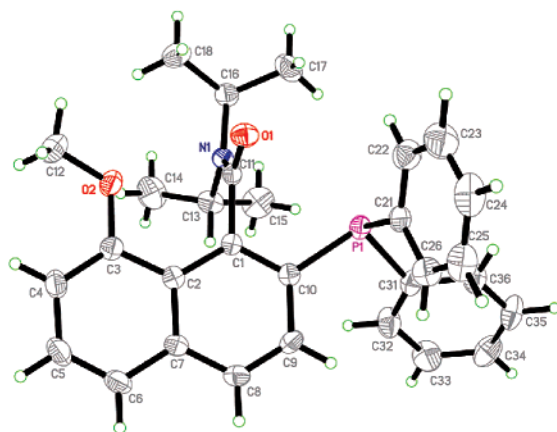
(10) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(11) Clayden, J.; McCarthy, C.; Helliwell, M. *Chem. Commun.* **1999**, 2059.

(a)



(b)

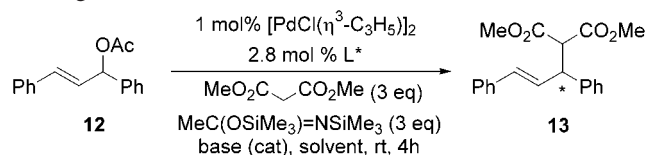


**Figure 2.** The X-ray crystal structures of (aS)-(+)-**9** (a) and (aR)-(+)-**10** (b).

completed within 4 h to afford (*S*)-**13** in 96% yield and in 78.6% ee (entry 1). We noted influence of the metal counterion on asymmetric induction. NaOAc (94.4% ee) and LiOAc (93.3% ee) gave better results than KOAc (78.6% ee) (entries 1–3). A solvent effect was not observed for AAA carried out in CH<sub>2</sub>Cl<sub>2</sub>, CH<sub>3</sub>CN, or toluene (entries 2, 4, and 6). However, using 2.5-fold of ligand to palladium, the reaction was slowed slightly and the ee of the product dropped to 80.3% (entry 5). The C8-benzyloxy ligand (aR)-(-)-**11** gave slightly lower enantioselectivity (90.2% ee, entry 7 versus entry 3). Diastereomers (aR)-(-)-**7** and (aS)-(+)-**8** represented the matched (87.4% ee) and mismatched (33.1% ee) combination, respectively (entries 8 and 9). Nevertheless, in all cases, the product stereochemistry is controlled by the axial chirality of the ligands.

We rationalize the enantioselectivity of AAA using (aS)-(-)-**10** in the cartoon **I** (Figure 3). Referring to the X-ray crystal structure of (aR)-(+)-**10** given in Figure 2b, the amide and naphthalene units are nearly perpendicular. They form a puckered “chiral wall” by adjusting the orientation of the phosphine phenyl groups upon formation of the palladium complex. As illustrated in **I**, on the rear side of the wall is

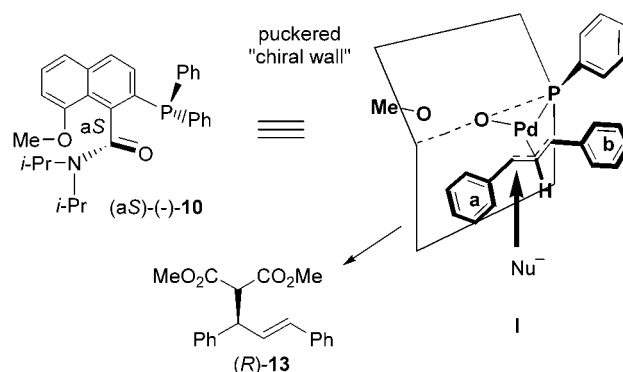
**Table 1.** Pd-Catalyzed AAA Using Nonbiaryl Atropisomeric P,O-Ligands **7**, **8**, **10**, and **11**



entry	L*	solvent	base	yield (%) <sup>a</sup>	ee (%), conf <sup>b</sup>
1	(aR)-(+)- <b>10</b>	CH <sub>2</sub> Cl <sub>2</sub>	KOAc	96	78.6, <i>S</i>
2	(aR)-(+)- <b>10</b>	CH <sub>2</sub> Cl <sub>2</sub>	NaOAc	89	94.4, <i>S</i>
3	(aS)-(-)- <b>10</b>	CH <sub>2</sub> Cl <sub>2</sub>	LiOAc	97	93.2, <i>R</i>
4	(aR)-(+)- <b>10</b>	CH <sub>3</sub> CN	NaOAc	89	94.4, <i>S</i>
5	(aR)-(+)- <b>10</b> <sup>c</sup>	CH <sub>3</sub> CN	NaOAc	89	80.3, <i>S</i>
6	(aR)-(+)- <b>10</b>	PhCH <sub>3</sub>	NaOAc	92	94.7, <i>S</i>
7	(aR)-(-)- <b>11</b>	CH <sub>2</sub> Cl <sub>2</sub>	LiOAc	99	90.2, <i>S</i>
8	(aR)-(-)- <b>7</b>	CH <sub>2</sub> Cl <sub>2</sub>	LiOAc	72	87.4, <i>S</i>
9	(aS)-(+)- <b>8</b>	CH <sub>2</sub> Cl <sub>2</sub>	LiOAc	81	33.1, <i>R</i>

<sup>a</sup> Isolated yield. <sup>b</sup> Enantiomeric excess and absolute configuration were determined by HPLC over a chiral stationary phase (see Supporting Information). <sup>c</sup> 2 mol % of Pd and 5 mol % of (aR)-(+)-**10** were used, and the reaction completed at room temperature after 5.5 h.

a phosphine phenyl group while the C8-methoxy sits to the front of the wall. They act as two “arms” to sterically guide



**Figure 3.** Proposed mechanism of enantioselectivity of (aS)-(-)-**10**.

the coordinated allyl unit. The latter takes the preferred *syn,syn*-geometry having the phenyl group (b) intrude into the space between the two phenyl groups on the phosphorus. The chelate shown in the cartoon **I** should be sterically favored. We assume attack of nucleophile occurs at the allyl terminus *trans* to the Pd–P bond as suggested in many previous studies on P,N-ligands.<sup>12</sup> Our model predicts formation of (*R*)-**13** in agreement with our experimental observation (Table 1, entry 3). The steric effect observed in

(12) (a) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, 35, 1523. (b) Brown, J. M.; Hulmes, D. J.; Guiry, P. J. *Tetrahedron* **1994**, 50, 4493. (c) Dawson, G. C.; Williams, J. M. J.; Coote, S. J. *Tetrahedron: Asymmetry* **1995**, 6, 2535. (d) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.;

entries 7–9 of Table 1 may be explained by the steric interaction between the C8-alkoxy and the nucleophile, resulting in nucleophilic attack at the allyl terminus *trans* to the Pd–O bond. However, it should be pointed out that the above discussion is a simple treatment as many factors may become dominant in stereodifferentiation under different reaction conditions.<sup>5c,6d,13</sup> The decreased ee using 2.5-fold ligand (Table 1, entry 5) may involve a distinct Pd complex where the phosphine may act as monodentate ligand.

In summary, we have synthesized a novel class of nonbiaryl atropisomeric P,O-ligands devoid of central chirality and have demonstrated their promising application in

AAA. Our current understanding on the amide-based phosphines is still limited. Further study on the catalysis and reaction scope of such ligands is in progress.

**Acknowledgment.** We thank the financial support provided by the Department of Chemistry, HKUST (through a postdoctoral fellowship to J.-T. Liu) and the Research Grants Council of the Hong Kong Special Administrative Region, China (through a Direct Allocation Grant, DAG99/00.SC14, and a Competitive Earmarked Research Grant, HKUST6219/01P).

**Supporting Information Available:** Experimental procedures, spectral data, and X-ray crystallographic analysis data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0258233

---

Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031. (f) Ward, T. R. *Organometallics* **1996**, *15*, 2836. (g) Blöchl, P. E.; Togni, A. *Organometallics* **1996**, *15*, 4125. (h) Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed. Eng.* **1997**, *36*, 2108.

(13) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.