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A Novel Class of Nonbiaryl Atropisomeric P,O-Ligands for Palladium-Catalyzed Asymmetric Allylic Alkylation†

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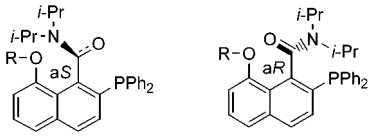
ABSTRACT



R = H, Me, $PhCH_2$, (1*S*)-(-)-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.[1] Bidentate chiral ligands enjoy wide application in both academic research and industrial processes because they form relatively rigid metal complexes and afford better stereodifferentiation in catalysis. For instance, C_2 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).[2] The latter is one of the most successful chiral P,P-ligand systems for asymmetric allylic alkylation (AAA) based on the "chiral pocket" concept.[2c,d,f] Non-C_2 symmetric chiral bidentate ligands, including chiral P,N-[3] and dinitrogen[2f,4]

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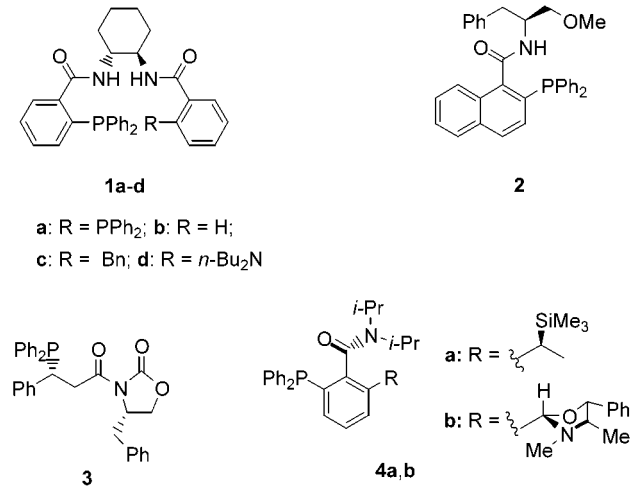
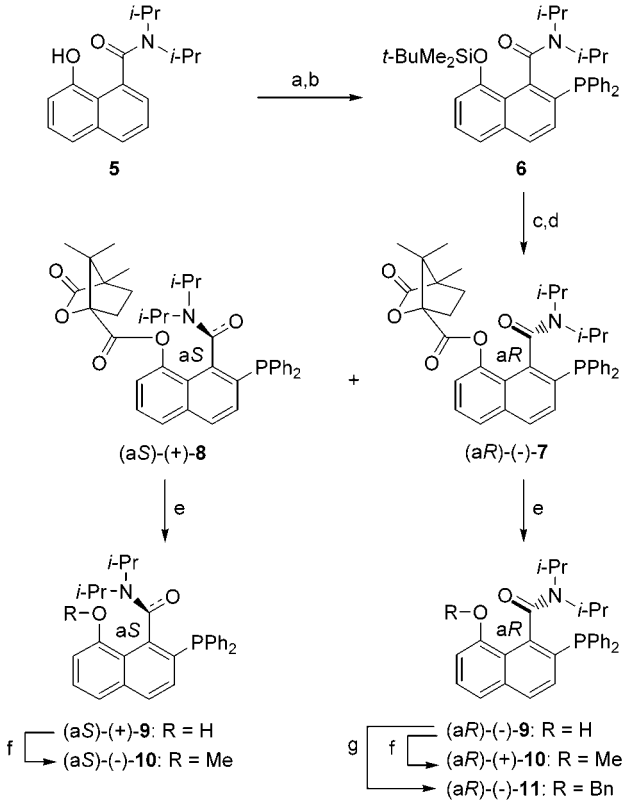


Figure 1. Structures of known P,P- and P,O-ligands for AAA.

ligands, give excellent regioselectivity and enantioselectivity in AAA. The diphosphine **1a** can form a P,O-chelate with palladium as well.[5] One such complex, being catalytically active, was confirmed by X-ray crystallographic analysis.[5b] Non-C_2 symmetric ligands **1b**,**c** were reported to give low and reversed ee's in AAA compared to that of **1a**.[5a] Interestingly, ligand **1d** competes between P,O- and P,N-chelation with palladium and gives up to ca. 80% ee's in AAA.[5c] Very recently, the amide-based P,O-ligands **2**−**4** were reported to give 74-90% ee's in AAA.[6] 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[7] P,O-ligands **9**−**11** devoid of central chirality and demonstrate their application in AAA.[8]

Our synthesis started with the known 1-naphthamide **5**[9] 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,[10] followed by reacting with PPh_2Cl 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[a]



[a] (a) *t*-$BuMe_2SiCl$, imidazole, DMF, 45 °C, 20 h (96%); (b) *s*-BuLi, THF, −78 °C, 1 h; then Ph_2PCl, −78 °C, 4 h (87%); (c) TBAF, THF, rt, 40 min (95%); (d) (1*S*)-(−)-camphanic chloride, DMAP, CH_2Cl_2, 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_2Cl_2, 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_2Cl_2−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.[11] 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

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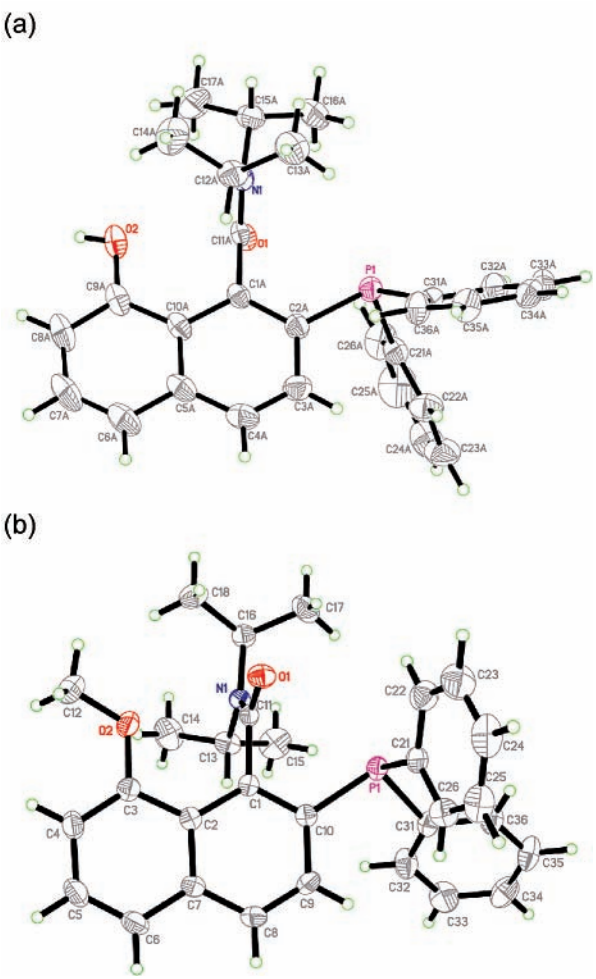
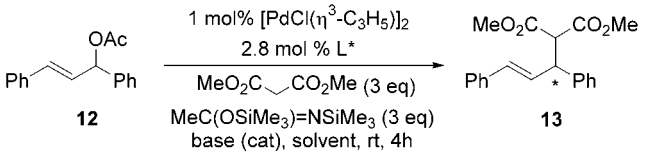


Figure 2. The X-ray crystal structures of (a*S*)-(+)-**9** (a) and (a*R*)-(+)-**10** (b).

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_2Cl_2, CH_3CN, 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 (a*R*)-(−)-**11** gave slightly lower enantioselectivity (90.2% ee, entry 7 versus entry 3). Diastereomers (a*R*)-(−)-**7** and (a*S*)-(+)-**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 (a*S*)-(−)-**10** in the cartoon **I** (Figure 3). Referring to the X-ray crystal structure of (a*R*)-(+)-**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 (%)[a]	ee (%), conf[b]
1	(a*R*)-(+)-**10**	CH_2Cl_2	KOAc	96	78.6, *S*
2	(a*R*)-(+)-**10**	CH_2Cl_2	NaOAc	89	94.4, *S*
3	(a*S*)-(−)-**10**	CH_2Cl_2	LiOAc	97	93.2, *R*
4	(a*R*)-(+)-**10**	CH_3CN	NaOAc	89	94.4, *S*
5	(a*R*)-(+)-**10**[c]	CH_3CN	NaOAc	89	80.3, *S*
6	(a*R*)-(+)-**10**	$PhCH_3$	NaOAc	92	94.7, *S*
7	(a*R*)-(−)-**11**	CH_2Cl_2	LiOAc	99	90.2, *S*
8	(a*R*)-(−)-**7**	CH_2Cl_2	LiOAc	72	87.4, *S*
9	(a*S*)-(+)-**8**	CH_2Cl_2	LiOAc	81	33.1, *R*

[a] Isolated yield. [b] Enantiomeric excess and absolute configuration were determined by HPLC over a chiral stationary phase (see Supporting Information). [c] 2 mol % of Pd and 5 mol % of (a*R*)-(+)-**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

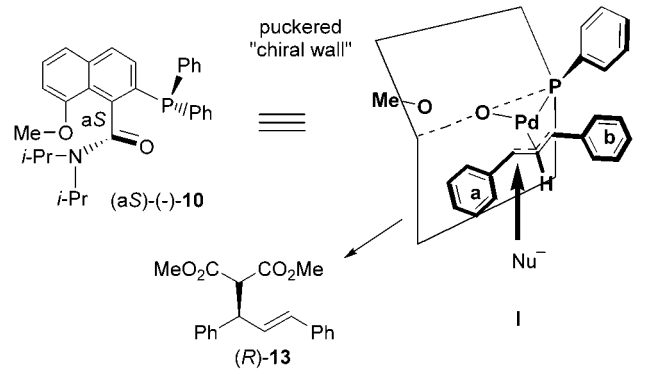


Figure 3. Proposed mechanism of enantioselectivity of (a*S*)-(−)-**10**.

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.[12] Our model predicts formation of (*R*)-**13** in agreement with our experimental observation (Table 1, entry 3). The steric effect observed in

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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.[5c,6d,13] 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.

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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.

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