Synthesis and Resolution of 3,3′-Disubstituted xylBINAP Derivatives and Their Application in Rhodium-Catalyzed Asymmetric Hydrogenation

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Abstract: A novel class of 3,3′-disubstituted xylBINAP ligands have been synthesized and tested in the hydrogenations of substituted olefins. This new substitution pattern has demonstrated that the 3,5-dialkyl meta effect and 3,3′-disubstitution can operate in a synergistic fashion in Rh-catalyzed hydrogenation of dehydroamino acids. Notably, (S_{ax})-**8** outperforms BINAP, xylBINAP and previously reported 3,3′-disubstituted BINAP derivatives in the hydrogenation of methyl *N*-acetamido cinnamate.

Key words: ligands, hydrogenations, asymmetric catalysis, homogeneous catalysis, rhodium

Asymmetric catalysis is one of the most powerful methods for forming an array of enantioenriched chiral structures. Transition-metal-based processes, which make up a large component of this field, rely on an organic ligand to impart chirality on the forming product during the catalytic cycle. Although a large pool of chiral ligands is available, there is still a need for new ligands, as not all of the existing ligands are suitable for all substrates. One method of developing new chiral ligands is to optimize the electronic and steric properties of an existing ligand through systematic modification of its framework.

Within the realm of transition-metal-mediated asymmetric processes, the utility of chiral biaryl diphosphine ligands has been widely demonstrated.[1] 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP; **1**) is one of the most commonly utilized chiral biaryl phosphines available, and its modification has been well documented.[2] In 2005, our group reported the first modification of the 3- and 3′-positions of BINAP.[3]

It was postulated that modifications made at the 3 and 3′ positions of BINAP would most drastically affect the steric and electronic properties of the ligand due to the proximity of these positions to the phosphorus atoms. To this end, we demonstrated that ligands **2**–**5** outperformed BINAP in the Rh-catalyzed hydrogenation of *N*-acetamido acrylic acid and its methyl ester, providing enantioselectivities of up to >99% ee for the resulting alanines (Figure 1). Also included in our initial report was the hydrogenation of methyl *N*-acetamido cinnamate using **1**–**5**. Performing this hydrogenation with BINAP led to poor enantioselectivity of the corresponding phenyl alanine but ee values as high as 74.7% were achieved by using ligand **4** with OC(O)*t*Bu groups in the 3 and 3′ positions of the binaphthalene framework. Although 3,3′-disubstitution provided an increase in enantioselectivity for the hydrogenation of methyl *N*-acetamido cinnamate, we saw the opportunity for further improvement.

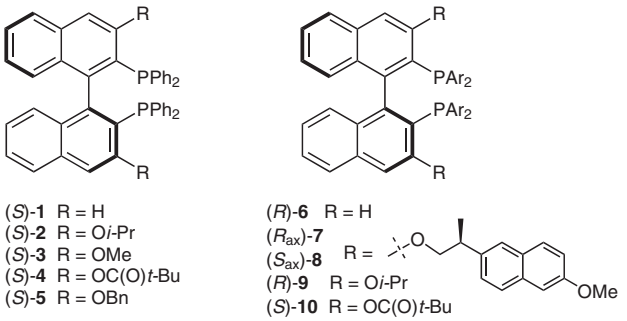

Figure 1 3,3′-Disubstituted BINAP and 3,3′-disubstituted xylBINAP derivatives

We envisioned that exchanging the phenyl rings in our 3,3′-disubstituted BINAP derivatives **2**–**5** for 3,5-dimethylphenyl (*m*-xylyl) rings would allow us to take advantage of the 3,5-dialkyl meta effect.[4] It has been demonstrated that using 3,5-dialkylphenyl substituents on phosphorus in place of simple phenyl rings, causes the chiral pocket to become more rigid and well-defined due to hindered rotation about the P–C_{ipso} bonds, which translates into higher catalyst selectivity in some systems. We were interested in exploring how increasing the steric congestion in both the 3 and 3′ positions of the binaphthyl skeleton, as well as on the phosphorus atoms, would affect the enantioselectivity of Rh-catalyzed hydrogenations of methyl *N*-acetamido cinnamic acid as well as other hydrogenation substrates. Herein, we report the synthesis and resolution of ligands **7**–**10** (Figure 1) and their application in the hydrogenation of dehydroamino acids and enamides.

Phosphinylation of 4-bromo-2-naphthol[5] (**11**) using di(3,5-dimethylphenyl)phosphinic chloride[6] in the presence of DMAP and Et_3N, afforded phosphinate ester **12** (Scheme 1). Lithiation-induced migration of the diarylphosphine oxide moiety on **12** provided appropriately substituted naphthalene ring **13**.[7] As in our previously reported synthesis, the presence of the hydroxyl group on the naphthalene ring is crucial for the optical resolution of the forthcoming biaryl axis. Out of a screen of several auxiliaries, naproxen-derived alcohol **14**[8] was found to be

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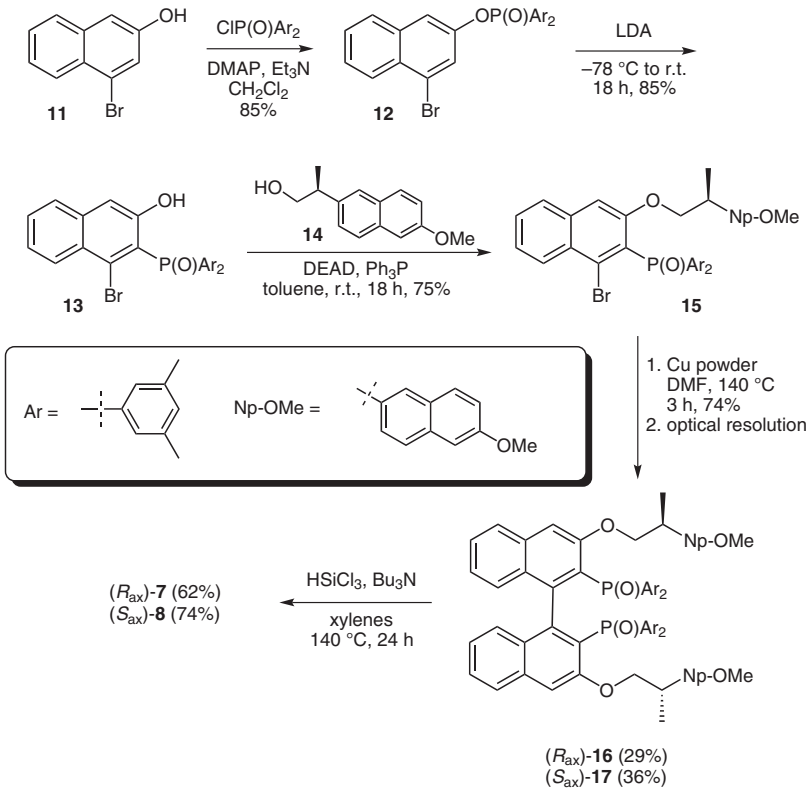


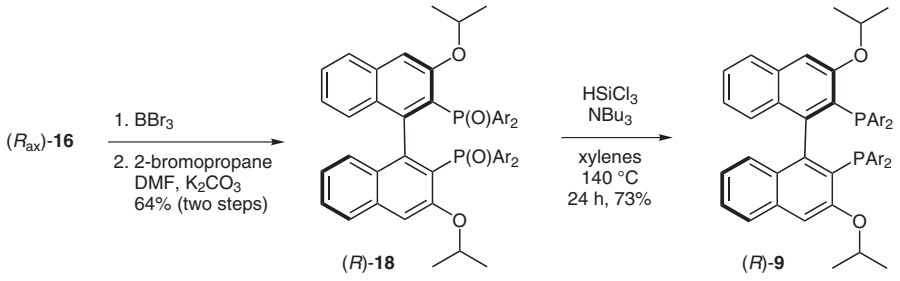
Scheme 1 Synthesis of diastereomeric 3,3′-disubstituted xylBINAP ligands (R_{ax})-**7** and (S_{ax})-**8**

most suitable for our purposes. Auxiliary **14** was coupled to naphthol **13** using standard Mitsunobu conditions.[9] Heating ether **15** in the presence of copper power facilitated biaryl bond formation to afford two diastereomeric diphosphine oxides (R_{ax})-**16** and (S_{ax})-**17**, which could be resolved using column chromatography[10] followed by recrystallization. Diphosphine oxides (R_{ax})-**16** and (S_{ax})-**17** were reduced independently with $HSiCl_3$ to afford diastereomeric 3,3′-disubstituted xylBINAP derivatives (R_{ax})-**7** and (S_{ax})-**8**. The absolute stereochemistry of the axis of chirality for (S_{ax})-**8** was obtained by X-ray crystallography of the corresponding Rh(I)(nbd)BF_4 adduct; the configuration assignment obtained for (S_{ax})-**8** was extended to the remainder of ligands in this report.

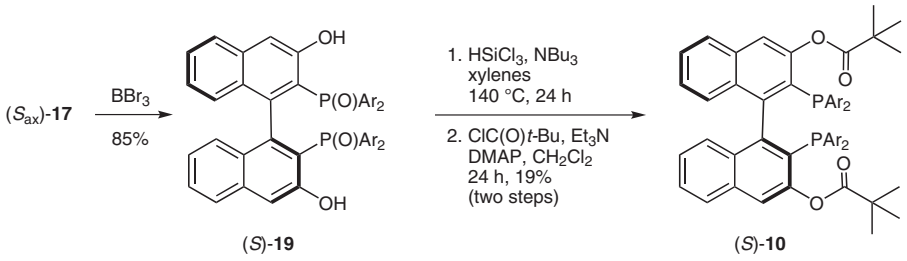
Synthetic routes to ligands (*R*)-**9** and (*S*)-**10** required removal of the chiral auxiliary, which was facilitated using BBr_3. Cleavage of the chiral auxiliary from (R_{ax})-**16** followed by alkylation with 2-bromopropane afforded diphosphine oxide **18** and hence the xylBINAP derivative (*R*)-**9** after phosphine oxide reduction (Scheme 2).[11]

Chiral auxiliary cleavage from (S_{ax})-**16** followed by acylation with trimethylacetyl chloride provided the diphosphine oxide of (*S*)-**10**, but reduction of this material resulted in a complex mixture of compounds with varying states of phosphine oxidation and ester cleavage. To circumvent this problem, after chiral auxiliary cleavage, dinaphthol (*S*)-**19** was isolated and then reduced under standard conditions.[12] Acylation of the crude reduction product afforded (*S*)-**10** (Scheme 3).

In order to assess the efficacy our new 3,3′-disubstituted xylBINAP derivatives **7**–**10** as ligands in Rh-catalyzed asymmetric hydrogenations, it was imperative that any potential 3,5-dialkyl meta effect was separated from the effect exerted by increased steric bulk in the 3 and 3′ positions. Thus, BINAP (**1**) and (*R*)-xylBINAP (**6**) were used as controls in order to establish the base 3,5-dialkyl meta effect.



Scheme 2 Synthesis of (R_{ax})-3,3′-(O*i*-Pr)$_2$-xylBINAP (**9**)



Scheme 3 Synthesis of (S_{ax})-3,3′-(OCO*t*-Bu)$_2$-xylBINAP (**10**)

Our initial examination began with the Rh-catalyzed hydrogenation of cyclic enamide **20** using BINAP derivatives **2**–**5** and xylBINAP derivatives **7**–**10** (Table 1). Control hydrogenations using (*S*)-BINAP and (*R*)-xylBINAP provided amide **21** in low ee's (16.8% and 13.2%, respectively). Of the BINAP derivatives screened, all but ligand **2** showed marked improvements over the parent BINAP, with ligand **5** [OC(O)*t*-Bu groups in the 3 and 3′ positions] showing the most promising result, providing **21** in 57.4% ee. Employing xylBINAP derivatives **7**–**10** provided no further enhancements to the observed ee for compound **21**. The best result out of this series was 48.7% ee, provided by (*R*)-**10**, which was nearly 10% lower in selectivity than that achieved by its BINAP analogue **5**.

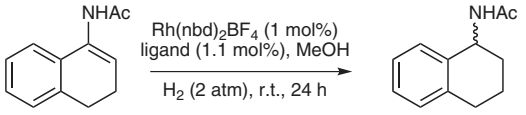
It is clear from the hydrogenation of enamide **20** that the xylyl groups in synthesized ligand **10** gave no additional improvement in enantioselectivity when compared to ligand **5**. Failure of **10** to further improve levels of enantioselectivity achieved by 3,3-disubstituted BINAP derivative **5** can be attributed to a slight negative 3,5-dialkyl meta effect,[13] which was observed in the comparison of the control ligands (**1** vs **6**, vide supra). It has been previously reported that too much steric bulk around the metal center may result in partial dissociation of either the diphosphine ligand or the substrate, resulting in diminished chirality transfer between the metal catalyst and substrate.[14]

Next, we moved on to the Rh-catalyzed hydrogenation of methyl *N*-acetamido cinnamate (**22**). When xylBINAP **6** was used as a ligand in the hydrogenation of **22**, it provided an enantioselectivity of 66.5%, nearly five times greater than that provided by BINAP (**1**; Table 2, entries 1 and 6), demonstrating that the 3,5-dialkyl meta effect is operational in this system. Our previous results showed that (*S*)-**2** and (*S*)-**4** were the best ligands out of the BINAP series and provided enantioselectivities of 23.2% and 74.7%, respectively, for the hydrogenation of **22**.[3]

In order to obtain a direct comparison to BINAP derivatives **2** and **4**, we chose to examine the xylBINAP analogues of **2** and **4** in the Rh-catalyzed hydrogenation of **20**. Using (*R*)-**9** as a ligand, provided **23** in 69.6% ee, representing a three-fold increase in selectivity when compared to the related BINAP ligand (*S*)-**2**, but comparable to the result obtained with (*R*)-**6** (entries 2, 4 and 7; Table 2). Ligand (*R*)-**10** provided phenyl alanine **23** in 73.8% ee, which was slightly higher than that provided by control **6** but comparable to that obtained with 3,3-disubstituted BINAP relative (*S*)-**4**. These results reinforce the idea that changing the steric environment provided by the chiral ligand can lead to improvements in enantioselectivity. However, this does not provide strong evidence that the 3,5-dialkyl meta effect and 3,3′-disubstitution are operating in a synergistic fashion, but rather that one may be having a stronger influence while the other lies dormant [i.e. 3,5-dialkyl meta effect dominates in (*R*)-**9** but is diminished when using (*R*)-**10**].

The introduction of chiral entity **14** into the 3 and 3′ positions of xylBINAP brings forth the possibility of double diastereodifferentiation in the enantio-determining step of these asymmetric hydrogenations. Ligands (R_{ax})-**7** and (S_{ax})-**8** did indeed show this phenomenon. Thus, simply changing the configuration of the chiral axis from *R* to *S*, without disturbing the configuration of the attached auxiliaries, improves the enantioselectivity of the hydrogena-

Table 1 Asymmetric Hydrogenation of Cyclic Enamide **20** Using BINAP Ligands **1**–**5** and xylBINAP Ligands **6**–**10**

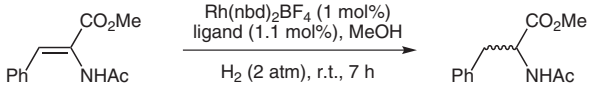


20 **21**

Entry[a,b]	Ligand	ee[c] (%)
1	(*S*)-**1**	16.8 (*S*)
2	(*S*)-**2**	5.2 (*R*)
3	(*S*)-**3**	20.3 (*R*)
4	(*S*)-**4**	35.3 (*S*)
5	(*S*)-**5**	57.4 (*R*)
6	(*R*)-**6**	13.2 (*R*)
7	(R_{ax})-**7**	33.9 (*R*)
8	(S_{ax})-**8**	20.9 (*S*)
9	(*R*)-**9**	36.9 (*S*)
10[d]	(*R*)-**10**	48.7 (*S*)

[a] All reactions proceeded with complete conversion.
[b] Catalyst formed in situ by premixing ligand with Rh(nbd)$_2$BF$_4$ in methanol for 30 min.
[c] Determined by chiral GC using a Cyclodex B column.
[d] The opposite configuration of ligand to that shown in Scheme 3 was used.

Table 2 Asymmetric Hydrogenation of Methyl *N*-Acetamido Cinnamic Acid (**22**) Using BINAP Ligands **1**–**5** and xylBINAP Ligands **6**–**10**



22 **23**

Entry[a,b]	Ligand	%ee[c]
1[d]	(*S*)-**1**	14.8 (*R*)
2[d]	(*S*)-**2**	23.2 (*S*)
3[d]	(*S*)-**4**	74.7 (*S*)
4	(*R*)-**6**	66.5 (*R*)
5	(R_{ax})-**7**	80.1 (*R*)
6	(S_{ax})-**8**	91.0 (*S*)
7	(*R*)-**9**	69.6 (*R*)
8[e]	(*R*)-**10**	73.8 (*R*)

[a] All reactions proceeded with complete conversion.
[b] Catalyst formed in situ by premixing ligand with $Rh(nbd)_2BF_4$ in methanol for 30 min.
[c] Determined by chiral HPLC using a Chiralcel OD column.
[d] Entries reproduced from ref 3 for purposes of comparison.
[e] The opposite configuration of ligand to that shown in Scheme 3 was used.

Table 3 Temperature Studies on the Hydrogenation of **22** Using BINAP Ligand **4** and xylBINAP Ligand **8**

Entry[a]	Ligand	Temp (°C)	Conv (%)[b]	%ee[c]
1	(*S*)-**4**	25	100	71.4 (*S*)
2	(*S*)-**4**	0	84	73.1 (*S*)
3	(*S*)-**4**	–20	82	69.2 (*S*)
4	(*S*)-**4**	–45	27	80.5 (*S*)
5	(S_{ax})-**8**	25	100	91.0 (*S*)
6	(S_{ax})-**8**	0	90	95.8 (*S*)
7	(S_{ax})-**8**	–20	53	>99 (*S*)
8	(S_{ax})-**8**	–45	0	–

[a] Catalyst formed in situ by premixing ligand with $Rh(nbd)_2BF_4$.
[b] Determined by GC–MS.
[c] Determined by chiral HPLC on a Chiralcel OD column.

tion of **22** from 80.1% to 91.0% (Table 2, entry 5 vs. Table 3, entry 5). Furthermore, both (R_{ax})-**7** and (S_{ax})-**8** outperform related ligands **2**–**5**, **9**, and **10**, and provide the highest ee's reported for this transformation with this class of BINAP ligands. This is interesting in itself, as the chiral centers of the pendant auxiliary are far removed from the phosphorus atoms in the solid state when these ligands are bound to Rh^I. We also found that lowering the temperature of the hydrogenation to –45 °C using **4**, afforded phenyl alanine **23** in 80.5% ee, albeit with only 27% conversion after seven hours (Table 3, entry 4). A similar temperature study using **8** revealed selectivities as high as >99% ee at –20 °C with 53% conversion (see entry 7). A synthetically useful 90% conversion and 95.8% ee was obtained at 0 °C (entry 6).

Lower temperatures for these hydrogenations not only provide higher enantioselectivities, but they also provide us with mechanistic insights. Traditionally, this type of Rh-catalyzed hydrogenation undergoes an 'anti-lock and key' mechanism in which it is the minor Rh-olefin diastereomer that undergoes hydrogenation.[15] This type of mechanism leads to higher enantioselectivities with higher temperatures. Our temperature studies reinforce the idea that these novel 3,3′-disubstituted BINAP and xylBINAP derivatives cause the Rh-catalyzed hydrogenation of **22** to undergo a mechanism different from that which was previously established.[16]

In summary, we have developed a synthetic route to 3,3′-disubstituted xylBINAP ligands. We have demonstrated that the additional steric bulk present in these ligands can either improve or shut down the selectivity of a given hydrogenation, depending on the substitution pattern of the ligand and the hydrogenation substrate. The introduction of chiral entities to the 3 and 3′ positions have also proven to be highly effective for the hydrogenation reactions.[17] We have provided more evidence for a different mechanistic mode for Rh-catalyzed hydrogenations when this class of ligands is utilized. We are exploring new ways of substituting the BINAP skeleton and are continuing to probe the mechanism of Rh-catalyzed hydrogenations using this novel class of diphosphine ligands.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(8) This alcohol is available from standard $LiAlH_4$ reduction of (+)-(*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid [(*S*)-naproxen].
(9) Attempts at forming the ether linkage via alkylative methods failed and resulted in elimination rather than substitution
(10) (S_{ax})-**8**, R_f = 0.35; (R_{ax})-**7**, R_f = 0.25 (EtOAc–hexanes, 35%)
(11) Cleavage of the chiral auxiliary followed by alkylation with MeI successfully afforded 3,3′-$(MeO)_2$-xylBINAP(O). However, exposing 3,3′-$(MeO)_2$-xylBINAP(O) to the reduction conditions caused demethylation. Use of alternative reduction conditions (AlH_3·THF) resulted in decomposition.
(12) We presumed that the sensitivity of the ester moieties was due to the increase of steric bulk around the phosphorus atoms. Reducing phosphine oxides in the presence of free hydroxy groups is known in the literature for sterically encumbered phosphorus atoms, see: Paruch, K.; Vyklický, L.; Wang, D. Z.; Katz, T. J.; Incarvito, C.; Zakharov, L.; Rheingold, A. L. *J. Org. Chem.* **2003**, *68*, 8539.
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(17) General Procedure for Rh-Catalyzed Asymmetric Hydrogenations: $Rh(nbd)_2BF_4$ (3.7 mg, 0.01 mmol), ligand (0.011 mmol) and MeOH (1 mL) were combined under an inert atmosphere and stirred for 30 min at room temperature. Olefin (1 mmol) was added with an additional aliquot of MeOH (1 mL). The reaction mixture was then subjected to three consecutive freeze/pump/thaw cycles on a double manifold (pump time = 10 min). Upon warming to room temperature, the reaction was placed under a hydrogen atmosphere (2 atm) for 7 h. Upon completion, volatiles were removed in vacuo and the remaining residue was passed through a plug of silica gel (hexanes–EtOAc, 1:1). Upon solvent evaporation, the isolated product was used directly for either chiral GC or chiral HPLC analysis.
Chiral GC data for *N*-(1,2,3,4-tetrahedronaphthalen-1-yl)acetamide(**21**): Cyclodex B column; isothermal 170 °C; t_{R1} [(*R*)-**21**] = 23.5 min, t_{R2} [(*S*)-**21**] = 24.4 min.
Chiral HPLC data for methyl α-acetamido cinnamate (**23**): Chiral HPLC, Chiralcel OD; hexane–*i*-PrOH, 9:1; 1.0 mL/min; t_{R1} [(*R*)-**23**] = 12.4 min, t_{R2} [(*S*)-**23**] = 16.3 min.