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Development of New *P*-Chiral *P*,π-Dihydrobenzooxaphosphole Hybrid Ligands for Asymmetric Catalysis

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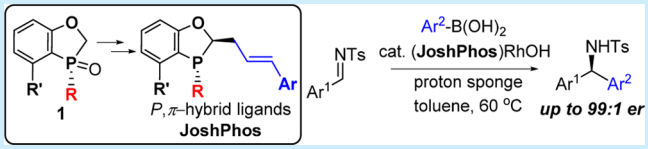
Supporting Information

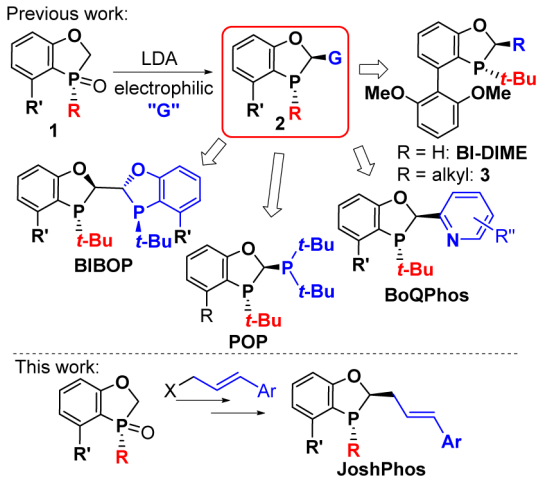
ABSTRACT: A new family of *P*-chiral *P*,π-hybrid ligands was prepared from the dihydrobenzooxaphosphole core. These new ligands were demonstrated to be both sterically and electronically tunable at the substituents on the phosphorus atom *and* the π-system of the ligand. Application of these new ligands to the catalytic asymmetric addition of boronic acids to imine electrophiles was shown to proceed with high levels of enantioinduction.



Asymmetric catalysis is an indispensable tool for the rapid and atom-economical[1] preparation of valuable chiral nonracemic organic compounds.[2] In particular, asymmetric catalytic processes employing a transition metal catalyst in conjunction with a chiral phosphine ligand have been widely developed and applied to the synthesis of complex molecules.[2,3] In general, the vast majority of these chiral ligands rely on chirality on the ligand backbone rather than directly at phosphorus (*P*-chirality).[4] It has been argued that placing the ligand chirality closer to the metal center may allow for better control of enantioselectivity,[4,5] and therefore, *P*-chiral ligands should be highly efficient ligands for asymmetric catalysis. While several *P*-chiral phosphine-based ligands are known,[6] the difficulty associated with the preparation of *P*-stereogenic compounds in enantiomerically pure form is likely the reason that there are significantly less of these ligands available compared to their "backbone chiral" counterparts.[7]

Recently, our laboratories have developed a series of useful *P*-chiral ligands (**2**, Scheme 1) derived from a dihydrobenzooxaphosphole core (**1**) prepared through alkyl/arylation of the deprotonated phosphine oxide **1**. This enables the synthesis of monophosphines (BI-DIME) useful in hindered[8] and asymmetric[9] cross-coupling reactions, bis(phosphines) (BIBOP, POP) useful for asymmetric hydrogenation[10,11] and propargylation,[12] and *P*,*N*-ligands (BoQPhos) useful for Ir-catalyzed asymmetric hydrogenation.[13] In an effort to further exploit the chiral motif of **1** for useful catalytic asymmetric processes, we envisioned that trapping the intermediate anion of **1** with a cinnamyl electrophile would allow access to *P*-chiral *P*,π-hybrid ligands (JoshPhos).[14] Additionally, because we have recently developed a powerful technique for the general synthesis of *P*-chiral phosphine oxides[15] that enables the synthesis of **1** with variable R groups, this new *P*,π-hybrid ligand class would be highly tunable, whereby both the steric and electronic properties of the ligand may be modulated by modification of the substituent on phosphorus (R) and/or the alkene (Ar).

Scheme 1. Dihydrobenzooxaphosphole Ligands



Herein we disclose the development of this new family of *P*-chiral *P*,π-hybrid ligands and describe their application in the Rh-catalyzed addition of boronic acids to imine electrophiles.

The preparation of a series of JoshPhos ligands was performed using the strategy outlined (Scheme 2). Deprotonation with LDA, followed by trapping with various cinnamyl chloride derivatives, led to the required oxides in moderate to good yields. Titanium-mediated reduction chemoselectively generated the desired ligands. For ligands containing aryl groups with strong electron-withdrawing groups (i.e., CF_3), the alkylation reaction using the corresponding cinnamyl derivative failed. For these ligands, cross-metathesis between allylated material **9** and the appropriate styrene derivative was employed.

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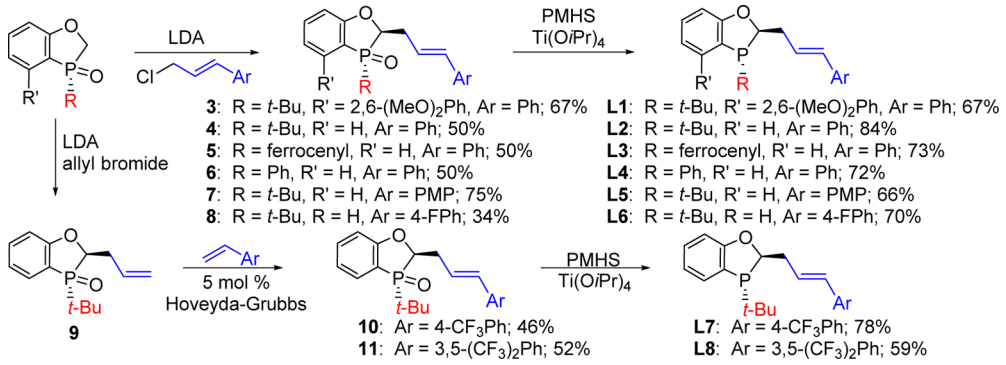
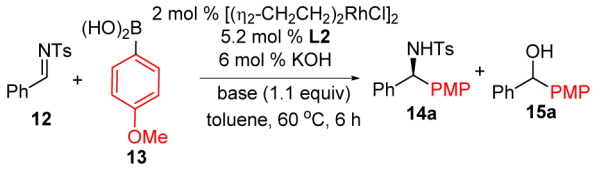
Scheme 2. Synthesis of *P*-Chiral *P*,π-Hybrid Ligands



With access to a series of *P*,π-hybrid ligands realized, we next examined their utility in asymmetric reactions. Because of the prevalence of chiral nonracemic amines in biologically active compounds and natural products, we first chose to investigate the Rh-catalyzed addition of boronic acids to imine electrophiles[16] to make these important functional groups in an enantioselective fashion. Initially, the reaction between tosyl imine **12** and boronic acid **13** was investigated (Table 1).

Table 1. Boronic Acid Addition to Benzaldimine[a]



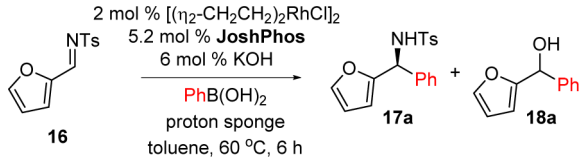
entry	base	% conv[b]	14a/15a[b]	% yield 14a[c]	er 14a
1[d]	TEA	83	81:19	56	99:1
2[d,e]	TEA	33	76:24	21	99:1
3	TEA	90	89:11	60	99:1
4	DIPEA	95	96:4	80	99:1
5	2,6-Lut	74	>97:3	55[f]	99:1
6	DMAP	<5		0	
7	DBU	45	76:24	22[f]	99:1
8[g]	DABCO	90	89:11	69	97:3
9	proton sponge	96	97:3	75	99:1

[a]Reaction conditions: imine (0.19 mmol), boronic acid (0.38 mmol), base (0.21 mmol), Rh (4 mol %), **L2** (5.2 mol %), 0.5 M KOH (6 mol %), toluene (0.78 mL), 60 °C, 6 h. [b]Determined by ^{1}H NMR spectroscopy. [c]Isolated yield. [d]2.0 equiv of base used. [e]KOH omitted. [f]NMR yield. [g]0.55 equiv of base used.

Ligand **L1** was first tested in this reaction, but no evidence for the formation of **14a** was observed. However, use of ligand **L2** did afford the desired product in modest yield, and we were excited to find that high levels of enantioinduction were obtained in the reaction (entry 1). Additionally, the yield of **14a** was significantly reduced in the absence of KOH (entry 2). The main byproduct of the reaction was a result of imine hydrolysis followed by addition of **13** (**15a**). Reducing the amount of TEA from 2.0 to 1.1 equiv led to a reduction in the amount of product **15a** (entry 1 vs 3). This result implied that the amine base affected the rate of hydrolysis of **12**, and therefore, we hypothesized that the yield of **14a** could be improved by tuning the added base. After a survey of amine bases (entries 3–9), it was discovered that bulky bases such as DIPEA (entry 4) or proton sponge (entry 9) gave reduced amounts of **15a** along with good yields of **14a**.

After having identified conditions that promoted the addition of boronic acid **13** to imine **12** in good yield with excellent enantiocontrol, we next examined this procedure with a more synthetically useful imine (Table 2).[17] Somewhat surprisingly,

Table 2. Boronic Acid Addition to Furfuralimine[a]



entry	JoshPhos	% conv[b]	17/18[b]	% yield 17[c]	er 17
1[d]	L2	42	62:38	26	96:4
2	L2	70	80:20	36	96:4
3	L3[e]	60	96:4	41	10:90
4	L4	>97	>97:3	95	86:14
5	L5	76	94:6	59	97:3
6	L6	94	81:19	62	97:3
7	L7	89	74:26	56	97:3
8	L8	>97	93:7	92	97:3

[a]Reaction conditions: imine (0.15 mmol), boronic acid (0.30 mmol), base (0.15 mmol), Rh (4 mol %), JoshPhos (5.2 mol %), 0.5 M KOH (6 mol %), toluene (0.62 mL), 60 °C, 6 h. [b]Determined by ^{1}H NMR spectroscopy. [c]Isolated yield. [d]DIPEA used in place of proton sponge. [e]The opposite enantiomer of **L3** used.

the optimal conditions for imine **12** using DIPEA as base were not suitable for heterocyclic aldimine **16** (entry 1). Use of proton sponge reduced the amount of hydrolysis product **18a** and improved the yield of **17a** slightly (entry 2). At this point, we examined the series of JoshPhos ligands we had prepared in this reaction (entries 3–8). Modifying the substituent on phosphorus from the bulky *tert*-butyl group to aromatic groups gave good to excellent reactivity, but enantioselectivity was reduced (entries 3 and 4). These results demonstrated the necessity of the *P*-*tert*-butyl moiety for high enantioselectivity and initially guided us to prepare the JoshPhos family (Scheme 2), whereby the electronic nature of the ligand was tuned by modulating the aryl group of the ligand alkene. Gratifyingly, the electronics of the alkene of the JoshPhos ligands had a significant impact on reactivity and could be used as a suitable tuning element for this series of new ligands (entries 5–8). Ligand **L8** containing the most electron-deficient π-system gave the highest yield of **17a** in conjunction with the highest enantioselectivity (entry 8).

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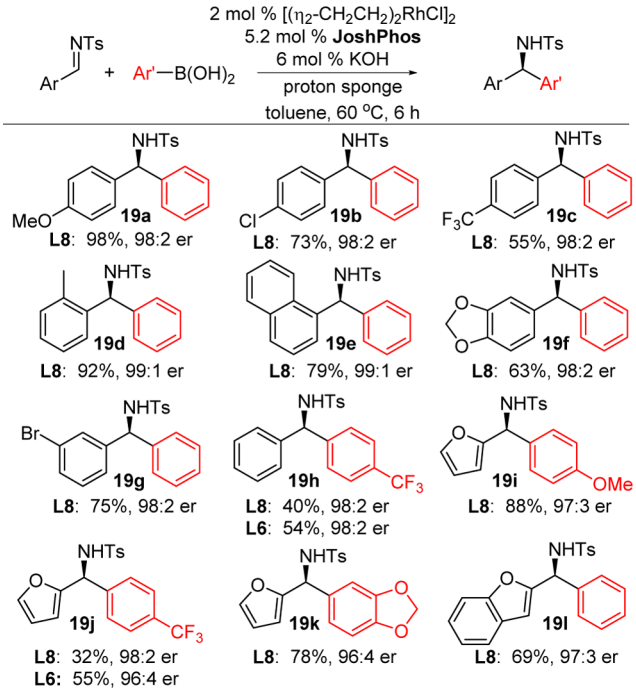
With identification of the optimal ligand for the addition of boronic acids to imines, we next explored the scope of this new catalytic system (Scheme 3). Electron-rich aldimines gave the highest yields (**19a**), while a reduction in yield was observed as the imine became more electron-poor due to the formation of increased amounts of hydrolysis products (compare **19a** vs **19b** vs **19c**). More sterically hindered aldimines bearing *ortho*-substitution participated well in the reaction (**19d** and **19e**). Aryl bromides were also tolerated in the reaction (**19g**). Using an electron-poor boronic acid nucleophile led to reduced reactivity (**19h** and **19j**). In these cases, the yield could be improved by switching to ligand **L6**.

Scheme 3. Addition of Boronic Acids to Tosyl Imines[a]



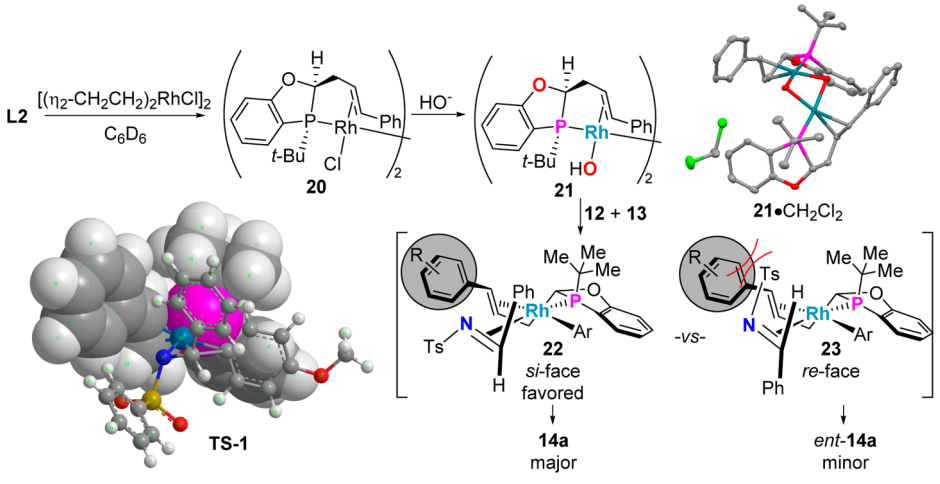
[a]Reaction conditions: imine (0.175 mmol), boronic acid (0.35 mmol), proton sponge (0.175 mmol), Rh (4 mol %), JoshPhos (5.2 mol %), 0.5 M KOH (6 mol %), toluene (0.71 mL), 60 °C, 6 h.

The mechanism of the Rh-catalyzed addition of boronic acids to a variety of unsaturated electrophiles has been well-established in the literature.[18b,19] To verify that the π-system of the JoshPhos ligand was involved in binding to the Rh atom of the catalyst, the reaction of an equimolar mixture of ligand **L2** and $[(\eta_2\text{-}CH_2CH_2)_2RhCl]_2$ was studied by NMR spectroscopy (Scheme 4). By ^{31}P NMR spectroscopy, free ligand was no longer present, and only a single phosphorus doublet resonance was observed at 107 ppm (J_{Rh-P} = 188 Hz). Furthermore, by ^{1}H NMR spectroscopy, the alkene protons of the free phosphine were shifted upfield to 3.91 and 4.30 ppm in the new complex, consistent with olefin binding. This data supports the formation of complex **20** that is likely a dimer based on similar reported complexes.[20] Subsequent reaction of **20** with hydroxide led to the formation of **21** that was characterized by X-ray crystallography (**21**•CH_2Cl_2).

The X-ray single-crystal structure of the $[(\mathbf{L2})RhOH]_2$ catalyst enabled insight into the mechanism of enantiomeric induction in these asymmetric processes. Transmetalation between **21** and $ArB(OH)_2$ followed by imine binding is expected to furnish intermediate complexes **22**/**23**. In these complexes, the preferred geometry about the Rh atom would place the Ar group *trans* to the olefin substituent of the JoshPhos ligand and the imine electrophile *trans* to the phosphorus group due to the "*trans*-effect".[21,22] The chirality of the JoshPhos ligand bound to Rh places the arene group of the ligand alkene in the "northwest" quadrant of the Rh complex. This orientation forces imine binding to be preferred from the *si*-face (**22**) to avoid a steric interaction between the aryl group on the ligand alkene and the tosyl group of the imine (**23**). Modeling of the transition state for the conversion of **22** to product using DFT[23,24] afforded **TS-1** that is in agreement with this proposal. Lastly, this catalytic system also affected the addition of phenyl boronic acid to cyclohexenone with high enantiocontrol. Modeling of this system using DFT was in complete agreement with the proposed stereochemical model.[25]

In conclusion, we have designed and developed a new family of *P*-chiral *P*,olefin hybrid ligands based on the dihydrobenzooxaphosphole core. To the best of our knowledge, these are the first *P*-chiral *P*,π-hybrid ligands reported. These new ligands were demonstrated to be both sterically and electronically tunable at the substituents on the phosphorus atom *and* the π-

Scheme 4. Catalyst Structure and Stereochemical Model



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system of the ligand. Additionally, this new series of ligands affected the addition of boronic acid nucleophiles to imine electrophiles with high levels of enantiocontrol, and a predictive stereochemical model was developed to rationalize the observed stereochemistry in these processes. Further application and development of this new family of *P*-chiral *P*,olefin ligands is under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Complete literature citations, experimental procedures, characterization data, and DFT methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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