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Steric Tuning of the Amidomonophosphane-Rhodium(I) Catalyst in Asymmetric Addition of Arylboroxines to *N*-Phosphinoyl Aldimines

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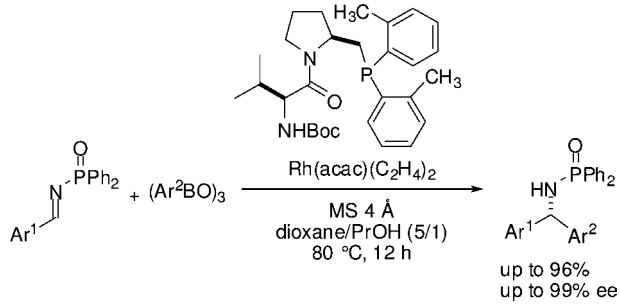
ABSTRACT



Highly enantioselective rhodium-catalyzed addition of arylboroxines to *N*-phosphinoylaldimines was realized by the steric tuning of a diphenylphosphorus moiety to a di(*o*-tolyl)phosphorus moiety of a chiral amidomonophosphane. The presence of MS 4 Å in a 5:1 solvent mixture of dioxane−propanol was essential to afford the corresponding diarylmethylamines in high yield.

Diarylmethylamines are key building blocks and potential intermediates for some biologically significant pharmaceuticals.[1] Asymmetric addition of arylmetal reagents to C=N double bonds of arylimines is a fundamentally important process[2] that provides convenient and versatile routes to this class of optically active amines.[3] In contrast to the extensively studied catalytic asymmetric alkylation reactions of imines,[4] however, the arylation counterpart has been less well explored. The earliest success of this type of arylation was the asymmetric addition of phenyllithium to *N*-(4-methoxyphenyl)imines with a substoichiometric amount of (−)-sparteine reported by Denmark.[4c] In 2000, Hayashi developed a brilliant catalytic asymmetric addition of arylstannane to *N*-sulfonylimines.[5] The toxic tin reagents were later replaced by aryltitanium reagents.[6] Bräse reported the asymmetric addition of diphenylzinc to *N*-formylimines, generated in situ,

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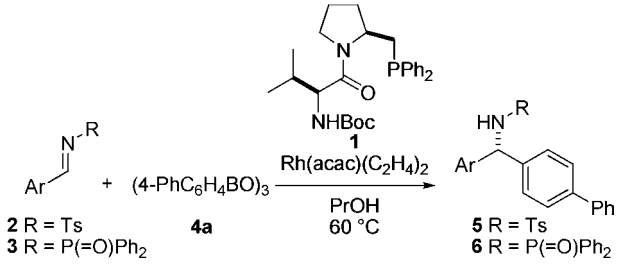
using a catalytic amount of an *N*,*O*-ligand.[7] We have also contributed to this research field by developing a rhodium-catalyzed asymmetric addition of arylboroxine to *N*-sulfonylimine using *N*-Boc-L-valine-connected amidomonophosphane **1** as a chiral ligand.[8] Arylboronic acid and arylboroxine are attractive arylating reagents because of their lower toxicity, stability in air and moisture, commercial availability, and good tolerance to a wide range of functional groups.[9] Other research groups have also reported the rhodium-catalyzed asymmetric addition of arylboronic reagents to *N*-tosylaldimines using ligands such as C_2-symmetric chiral diene,[10] a spirocyclic phosphite,[11] or *N*-linked bidentate phosphoramidite.[12] Although these methods yield products with high enantioselectivity, the conditions required for the reductive removal of a tosyl group from nitrogen, such as samarium(II) iodide with HMPA in refluxing THF, are incompatible with electron-accepting functional groups, e.g. carbonyl, nitro, and halogens. Recently, the rhodium-catalyzed asymmetric addition of arylboronic acid to *N*-diphenylphosphinoyl-(Dpp)[13] and *N*-Boc-imines[14] generated in situ using chiral bisphosphine ligand and to *N*-sulfamoylimines[15] using phosphoramidite ligands were reported, but the scope of *N*-Dpp-imines has not been examined. Herein, we report a highly enantioselective rhodium-catalyzed addition reaction of arylboroxines to *N*-Dpp-arylimines, utilizing a sterically tuned amidomonophosphane as the ligand, which provides a versatile entry to a wide range of optically active diarylmethylamines.

The initial stage of our study was performed using 1.67 equiv of biphenylboroxine **4a** in the presence of a chiral amidomonophosphane **1**−Rh complex (6 mol %) in propanol, the conditions we previously developed for the enantioselective addition of *N*-tosylimines **2** (Table 1).[8]

Table 1. Rh(I)-**1**-Catalyzed Asymmetric Arylation of *N*-Tosyl- and *N*-Dpp-imines **2** and **3** with 4-Biphenylboroxine **4a**[a]



entry	imine	Ar	R	time (h)	yield[b] (%)	ee[c] (%)
1	**2a**	Ph	Ts	3	83	66
2	**3a**	Ph	P(=O)Ph_2	3	95	70
3	**2b**	2-TMSC_6H_4	Ts	3	98	91
4	**3b**	2-TMSC_6H_4	P(=O)Ph_2	3.5	74	81

[a] Reaction of 0.2 mmol of **2** or **3** with 6 mol % of Rh(acac)(C_2H_4)$_2$ and 6.6 mol % of **1** at 80 °C. [b] Isolated yield. [c] Determined by chiral HPLC.

Reaction of Dpp-imine **3a** was complete within 3 h, and the addition product **6aa**[16] with 70% ee was obtained in 95% yield (entry 2). This enantioselectivity paralleled that of tosylimine **2a** (entry 1). The 2-TMSC_6H_4 imine **3b**, which was effective in the reaction of tosylimine **2b** (91% ee, entry 3), slightly improved the enantioselectivity to 81% ee (entry 4). Because the enantioselectivity was not satisfactory for *N*-Dpp-imines **3** (entries 2 and 4), however, steric tuning of the amidophosphane was the target of the second stage of the study based on the stereochemical analysis.

The X-ray crystal structure of rhodium(I)−**7**[17] suggests that the C═N double bond of *N*-Dpp-imine **3a** coordinates to rhodium(I)[18] on the *Re*-face (A) to give the product with the observed *S*-configuration (Figure 1). Coordination on the *Si*-face (B) is unfavorable due to steric repulsion between the axial phenyl of the phosphorus and the phenyl group of Dpp. This analysis indicated that the bulkiness of the phenyl

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(16) The first "**a**" and second "**a**" of **6aa** are derived from the suffixes of **3a** and **4a**, respectively.

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(18) The Ar-Rh(I) species is formed by transmetalation between rhodium(I) and arylboroxine at the trans side to phosphorus, which is the most vacant coordination site and influenced by the trans effect of phosphine. See ref 17.

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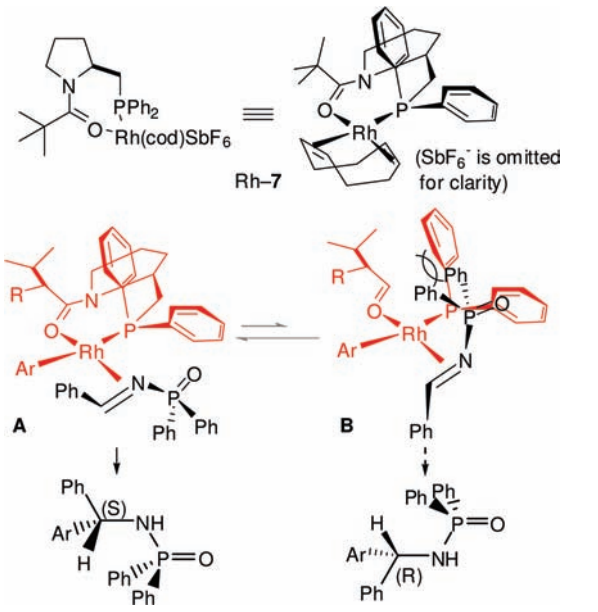
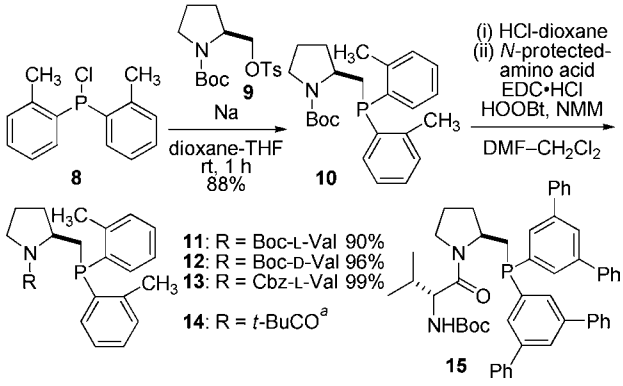


Figure 1. Stereochemical analysis of enantioselective pathway.

group of the phosphorus favors **A** over **B**, and therefore, increased bulkiness should improve the enantioselectivity of the reaction.

The sterically tuned di(*o*-tolyl)phosphanes **11**−**14** and bis(3,5-diphenylphenyl)phosphane **15** were synthesized as shown in Scheme 1. Commercially available di(*o*-tolyl)phosphoryl chloride **8**[19] was coupled with **9** to give *N*-Boc phosphane **10**. The *N*-Boc group was then replaced with *N*-Boc-L- or -D-Val (**11** and **12**), *N*-Cbz-L-Val (**13**), and a pivaloyl group (**14**). Bis(3,5-diphenylphenyl)phosphane **15** was also synthesized in the same manner.[20]

Scheme 1. Synthesis of Sterically Tuned Ligands **11**−**15**



[a] Synthesized from **10** in 91% yield by (i) HCl−dioxane and (ii) PivCl.

The reaction of biphenylboroxine **4a** and *N*-Dpp-imine **3a** was catalyzed by Rh(I)-**11** to give **6aa** with 90% ee (Table 2, entry 1). The reaction was sluggish, however, and did not reach completion after 12 h, even at 80 °C. The bulkiness, which was increased by *o*-methyl groups, would prevent imine **3a** coordination to the rhodium metal. Very bulky bis(3,5-diphenylphenyl)phosphane **15** was not effective and resulted in poor yield and enantioselectivity (entry 2). Screening of the reaction solvents revealed that a 5:1 mixture of dioxane and propanol at 80 °C afforded **6aa** with excellently high 98% ee in 81% yield (entries 3 and 4). Almost the same selectivity was observed with the same facial selectivity in the reactions using *N*-Boc-L-valine-connected ligand **11** (81%, 98% ee), *N*-Boc-D-valine-connected ligand **12** (80%, 95% ee), and *N*-Cbz-L-valine-connected ligand **13** (84%, 96% ee) (entries 4−6). Ligand **14** under the same conditions gave **6aa** with 90% ee in 61% yield (entry 7). These results indicated the *o*-methyl groups on the benzene ring of phosphorus are very helpful for producing high enantioselectivity and that the amide group of the pyrrolidine nitrogen was not crucial for enantiofacial selectivity.

The significant amount of benzaldehyde (entries 1−7) observed indicates hydrolysis by water, which would be generated by alcoholysis of boroxine.[21,22] Actually, the addition of 5 equiv of water resulted in hydrolysis of the imine **3a**, and no addition product **6aa** was obtained (entry 8). In the presence of MS 4 Å, the yield of **6aa** was greatly improved to 93%, and no benzaldehyde was observed, even in the crude mixture of the reaction (entry 9). The use of alcoholic solvent was important; the reaction in dioxane as a sole solvent gave a yellow suspension due to insolubility of the boroxine **4a**, providing **6aa** in poor yield (9%; entry 10). The use of MS 4 Å as an additive in propanol did not increase the chemical yield (entry 11).

Having established the optimal protocol (Table 2, entry 9), arylation with other arylboroxines and *N*-Dpp-aldimines was examined (Table 3). Arylation of **3a** with *p*-methyl-, *p*- and *m*-methoxy-, and *p*-chlorophenylboroxines proceeded satisfactorily in high to excellent yield (88−96%) and excellent enantioselectivity (95−98% ee) (entries 1−4). This high performance indicates that the arylboroxines bearing both electron-donating and -withdrawing substituents on the phenyl group are tolerated in this arylation reaction. Excellent enantioselectivity (98% ee) was also observed with bulky 4-biphenylboroxine (entry 5). This rhodium-catalyzed asymmetric arylation was applicable to a variety of *N*-Dpp-imines **3**. Arylation of **3c** and **3d** derived from arylaldehydes bearing an electron-donating *p*-methyl- or a sterically demanding *o*-methylphenyl group gave the corresponding addition products in high yield (86−95%) and high to excellent enantioselectivity (94−99% ee; entries 7−9). Arylation of electron-deficient imines **3e** and **3f** bearing a chloro or a trifluoromethyl group at

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(22) Another possibility is a boronic acid impurity in the boroxines, which were prepared by heating the corresponding boronic acids at 120 °C under 10 mmHg for 12 h. If the boronic acids remain impure, water is generated by forming boroxine in situ. The use of **4a**, dried at 220 °C under 0.5 mmHg for 4 h prior to use, however, did not make a significant difference (**6aa**, 82%, 98% ee; PhCHO, 6%) under the conditions shown in Table 2, entry 4. Therefore, this possibility was excluded.

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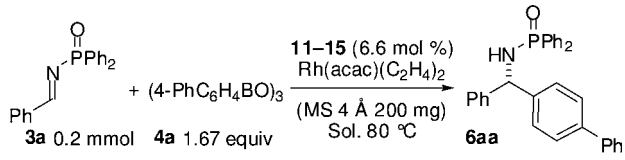
Table 2. Asymmetric Arylation of *N*-Phosphinoylbenzaldimine **3a** with 4-Biphenylboroxine **4a** Catalyzed by Ligand−Rh(I)[a]



3a 0.2 mmol **4a** 1.67 equiv **6aa**

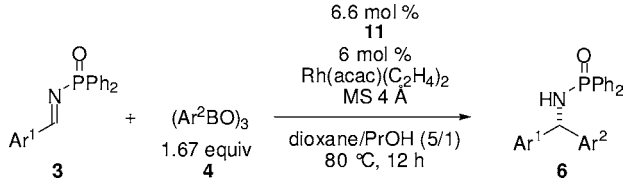
entry	ligand	solvent	MS 4 Å	time (h)	yield[b] (%)	ee[c] (%)	**3a** (%)	PhCHO (%)
1	**11**	PrOH	none	12	48	90	6	18
2[d]	**15**	PrOH	none	18	22	36	42	30
3	**11**	PhMe/PrOH (10/1)	none	12	60	94	5	10
4	**11**	dioxane/PrOH (5/1)	none	12	81	98	0	9
5	**12**	dioxane/PrOH (5/1)	none	12	80	95	0	12
6	**13**	dioxane/PrOH (5/1)	none	12	84	96	0	11
7	**14**	dioxane/PrOH (5/1)	none	12	61	90	0	30
8	**11**	dioxane/H_2O[e]	none	12	0		8	92
9	**11**	dioxane/PrOH (5/1)	200 mg	12	93	98	0	0
10	**11**	dioxane	200 mg	12	9[f]	nd	52	39
11	**11**	PrOH	200 mg	12	17	89	39	9

[a] Reaction of 0.2 mmol of **3a** with 6 mol % of Rh(acac)(C_2H_4)$_2$ and 6.6 mol % of amidophosphane **11**−**15** at 80 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The reaction was run at 60 °C. [e] 1 mmol of water was added. [f] Based on the crude ^{1}H NMR.

the *para* position of the benzene ring gave the addition products with 90−96% ee (entries 10−12). 1-Naphthaldimine **3g**, 2-naphthaldimine **3h**, and 2-furancarboaldimine **3i** were also applicable to give the products with 86%, 97%, and 92% ee, respectively (entries 13−15).

It is also important to note that catalyst loading could be reduced to 1 mol % to give **6aa** with 96% ee in 76% yield (entry 6).

Table 3. Amidomonophosphane−Rh-Catalyzed Asymmetric Arylation of *N*-Dpp-imines **3**



3 **6**

entry	Ar^1	Ar^2	yield/%	ee/%
1	Ph (**3a**)	4-$CH_3C_6H_4$ (**4b**)	96 (**6ab**)	98
2	Ph (**3a**)	4-$MeOC_6H_4$ (**4c**)	92 (**6ac**)	98
3	Ph (**3a**)	3-$MeOC_6H_4$ (**4d**)	88 (**6ad**)	95
4	Ph (**3a**)	4-ClC_6H_4 (**4e**)	90 (**6ae**)	98
5	Ph (**3a**)	4-PhC_6H_4 (**4a**)	93 (**6aa**)	98
6[a]	Ph (**3a**)	4-PhC_6H_4 (**4a**)	76 (**6aa**)	96
7	4-$CH_3C_6H_4$ (**3c**)	4-PhC_6H_4 (**4a**)	93 (**6ca**)	99
8	2-$CH_3C_6H_4$ (**3d**)	Ph (**4f**)	86 (**6df**)	94
9	2-$CH_3C_6H_4$ (**3d**)	4-PhC_6H_4 (**4a**)	95 (**6da**)	95
10	4-ClC_6H_4 (**3e**)	Ph (**4f**)	80 (**6ef**)	92
11	4-ClC_6H_4 (**3e**)	4-PhC_6H_4 (**4a**)	85 (**6ea**)	96
12	4-$CF_3C_6H_4$ (**3f**)	4-PhC_6H_4 (**4a**)	83 (**6fa**)	90
13	1-Naph (**3g**)	4-$CH_3C_6H_4$ (**4b**)	76 (**6gb**)	86
14	2-Naph (**3h**)	4-$CH_3C_6H_4$ (**4b**)	92 (**6hb**)	97
15	2-furyl (**3i**)	4-$CH_3C_6H_4$ (**4b**)	84 (**6ib**)	92

[a] Rh(acac)(C_2H_4)$_2$ (1 mol %) and **11** (1.1 mol %) were used.

The *N*-phosphinoyl group was readily removed without any racemization under the reported mildly acidic conditions (HCl in dioxane/MeOH at room temperature).[23] The products **6aa** and **6ac** gave the corresponding diarylmethylamines[24,6] in 97% and 93% yield, respectively. The stereochemistry of **6aa** was determined by applying Mosher's method to this deprotected amine. The stereochemistry of **6ac** and **6ae** was confirmed by comparing the specific rotation to those reported.[13a] The stereochemistry of the other products was tentatively assigned by analogy.

In conclusion, steric tuning of the amidophosphane ligand improved the enantioselectivity up to 99% ee in Rh(I)-catalyzed asymmetric addition of *N*-Dpp-aldimines with arylboroxines. The increased bulkiness of the ligand slowed the reaction rate, causing competitive hydrolysis of the imine. The removal of water generated in situ by the addition of MS 4 Å was important to obtain the addition product in good yield. The *N*-Dpp group was easily removed to form diarylmethylamines under a mildly acidic condition. This method provides a convenient and versatile access to a variety of optically active diarylmethylamine derivatives.

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Supporting Information Available: Experimental details; analytical and spectral characterization data of the ligands and the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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