Enantioselective Rhodium-Catalyzed Addition of Arylboronic Acids to Aldehydes Using Chiral Spiro Monophosphite Ligands
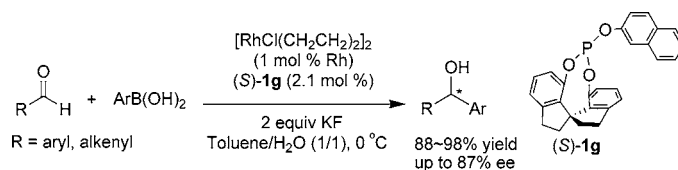
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ABSTRACT

Highly efficient rhodium-catalyzed asymmetric addition of arylboronic acids to aldehydes has been realized by using chiral spiro monophosphite ligands, affording diarylmethanols in excellent yields and good enantiomeric excesses.

Catalytic asymmetric carbon−carbon bond formation was one of the most studied subjects in the past few decades. In these studies, the enantioselective addition of aryl organometallic reagents to aldehydes remains to be an extremely attractive topic because the products, secondary aryl alcohols, are important intermediates for the synthesis of biologically and pharmaceutically active compounds.[1] Recently, great progress has been achieved in the amino alcohol mediated enantioselective addition of pre-prepared or in situ generated arylzinc reagents to aldehydes.[2] However, the examples for the transition-metal-catalyzed asymmetric additions of aryl organometallic reagents to aldehydes are quite limited.[3] In 1998, Miyaura and co-workers initially reported the enantioselective Rh-catalyzed addition of phenylboronic acid to naphthaldehyde by using the (*S*)-MeO−MOP ligand giving naphthylphenylmethanol in 78% yield and 41% ee.[3a] To the best of our knowledge, this result is so far the highest enantioselectivity for Rh-catalyzed addition of aryl organometallic reagents to aldehydes.[4] Thus, the search for efficient chiral ligands to achieve high enantioselectivity in this very useful reaction is the goal of many efforts.

Recently, we have developed new types of monodentate chiral phosphoramidites and phosphonites based on 1,1′-spiro-biindane-7,7′-diol and demonstrated that they were

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highly efficient ligands in asymmetric Rh-catalyzed hydrogenation[5] and other asymmetric reactions.[6] Herein, we report an effective protocol for asymmetric rhodium-catalyzed addition of arylboronic acids to aldehydes using chiral spiro phosphite ligands **1** (Figure 1), providing diarylmethanols in excellent yields with up to 87% ee.
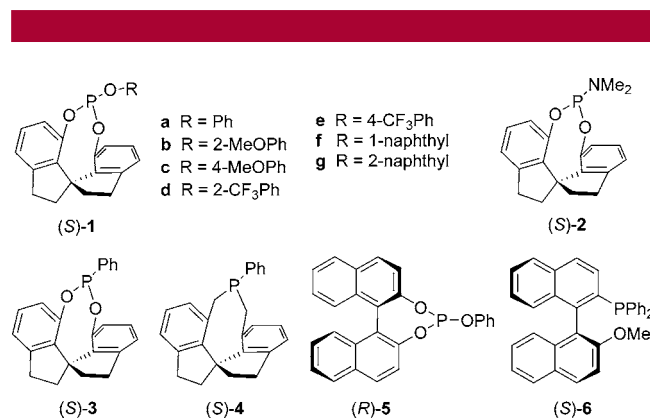

Figure 1. Tested chiral monodentate phosphorus ligands.

Initial studies dealt with the reaction of 1-naphthaldehyde and 2 equiv of $PhB(OH)_2$ in DME/H_2O (1:1) in the presence of 1.5 mol % of $[RhCl(CH_2CH_2)_2]_2$ and 6 mol % of (S)-**1a**. After reaction for 48 h at 60 °C, the addition product **9a** was isolated in 37% yield and 42% ee (Table 1, entry 1).

Table 1. Rhodium-Catalyzed Addition of Phenylboronic Acid to 1-Naphthaldehyde

entry	ligand	solvent	add.[a]	temp/time (°C)/(h)	yield (%)[b]	ee (%)[c]
1	**1a**	DME		60/48	37	42
2	**1a**	dioxane		60/48	45	52
3	**1a**	THF		60/48	60	55
4	**1a**	DCE		60/48	67	56
5	**1a**	toluene		60/48	77	62
6	**1a**	toluene	KF	rt/3	95	70
7	**1b**	toluene	KF	rt/24	67	54
8	**1c**	toluene	KF	rt/6	93	68
9	**1d**	toluene	KF	rt/10	85	60
10	**1e**	toluene	KF	rt/3	95	71
11	**1f**	toluene	KF	rt/6	85	61
12	**1g**	toluene	KF	rt/3	95	74
13[d]	**1g**	toluene	KF	0/7	95	80
14	**2**	toluene	KF	rt/24	48	54
15	**3**	toluene	KF	rt/24	47	42
16	**4**	toluene	KF	rt/24	30	39
17	**5**	toluene	KF	rt/24	59	49
18	**6**	toluene	KF	rt/24	28	52

[a] 2 equiv. [b] Isolated yield. [c] Determined by chiral HPLC using a chiralcel OD column. Absolute configuration is R. [d] Carried out with 1 mol % of rhodium and 2.1 mol % of (S)-**1g**.

Variation of the solvent showed that the 1:1 mixture of toluene/H_2O was the best choice of solvent. It was delightful to find that the addition of 2 equiv of KF as additive boosted both the yield and enantiomeric excess of addition product **9a** to 95% and 70%, respectively (entry 6). Next, we investigated different rhodium complexes as precursors in the addition reaction and found that all tested rhodium complexes had similar enantioselectivities, whereas the $[RhCl(CH_2CH_2)_2]_2$ gave the highest yield.

For searching more efficient chiral ligands, we then synthesized a number of spiro monophosphites **1** with different R groups, illustrated in Figure 1.[7] Among them, **1g** (R = 2-naphthyl) was found to be the best ligand which could proceed the addition reaction smoothly even with 1 mol % of rhodium at 0 °C, giving the addition product **9a** in excellent yield (95%) and good ee value (80%) (entry 13). Besides spiro phosphite ligands **1**, other monodentate ligands **2−6** with a spiro-biindane or binaphthyl backbone were also tested and none of them afforded a result superior to the ligand **1g** (entries 14−18), indicating that the rigid spiro phosphite ligands with a large dihedral angle benefit the formation of an effective catalyst with high activity and asymmetric induction ability.

Having optimized reaction conditions, we examined the reactions with various aldehydes and arylboronic acids and the results are summarized in Table 2. The arylations with

Table 2. Rhodium-Catalyzed Addition of Arylboronic Acids to Aldehydes

entry	**7** (R =)	**8** (Ar =)	yield (%)[a]	ee (%)[b,c]
1	2-Me−Ph	Ph	94 (**9b**)	80 (R)
2	2-Cl−Ph	Ph	97 (**9c**)	82 (R)
3	2-Br−Ph	Ph	96 (**9d**)	83 (R)
4	2-NO₂−Ph	Ph	91 (**9e**)	73 (R)
5	4-MeO−Ph	Ph	90 (**9f**)	65 (R)
6	4-Cl−Ph	Ph	94 (**9g**)	62 (R)
7	4-CF₃−Ph	Ph	96 (**9h**)	70 (R)
8	trans-PhCH=CH	Ph	96 (**9i**)	75 (S)
9	2-Cl−Ph	4-Me−Ph	94 (**9j**)	84 (R)
10	2-Cl−Ph	4-F−Ph	98 (**9k**)	83 (R)
11	2-Cl−Ph	4-Ac−Ph	88 (**9l**)	85 (R)
12	2-Cl−Ph	3-MeO−Ph	91 (**9m**)	80 (R)
13	2-Cl−Ph	2-Me−Ph	93 (**9n**)	63 (R)
14	2-Cl−Ph	2-thienyl	98 (**9o**)	71 (S)
15	2-Cl−Ph	2-naphthyl	96 (**9p**)	83 (R)
16	2-Br−Ph	4-MeO−Ph	94 (**9q**)	85 (R)
17	2-Br−Ph	4-Ph−Ph	94 (**9r**)	87 (R)

[a] Isolated yields. [b] Determined by chiral HPLC (see Supporting Information). [c] Absolute configuration was assigned by comparison to the literature data or by consideration of the stereochemical reaction pathway (see text).

either electron-rich or electron-deficient benzaldehydes proceeded smoothly to afford the corresponding diarylmethanols in excellent yields. In the case of ortho-substituted benzal-

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dehydes, good enantioselectivities were achieved (Table 2, entries 1−4). In the reactions with para-substituted benzaldehydes, relatively lower ee values were obtained (entries 5−7), showing that the steric hindrance instead of the electronic effect of substituents on the phenyl ring of benzaldehyde played a major role in the enantiocontrol. In addition to the benzaldehyde derivatives, *trans*-cinnamaldehyde can also react with phenylboronic acid to produce *trans*-phenylvinylphenylmethanol in 96% yield and 75% ee (entry 8).

A variety of arylboronic acids were used as an aryl source in the reaction with ortho-halogenated benzaldehydes. It is worthy to note that the meta- and para-substituted phenylboronic acids regardless of the electronic nature of the substituent could be transferred to aldehydes, affording the corresponding diarylmethanols in excellent yields and 80−87% ee (entries 9−12, 16, and 17). However, the reaction of *ortho*-methyl phenylboronic acid had a lower enantioselectivity (63% ee, entry 13), indicating that the steric hindrance of the arylboronic acid reagent is also the major factor in the control of the enantioselectivity of the reaction. The additions of 2-thiopheneboronic acid and 2-naphthylboronic acid to 2-chlorobenzaldehyde were also examined, and the desired addition products were obtained in 98% yield with 71% ee and 96% yield with 83% ee, respectively (entries 14 and 15).
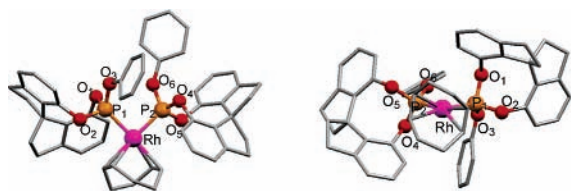

Figure 2. Crystal structure of [Rh(COD)((*S*)-**1a**$_2$)]BF$_4$. Anion was omitted for clarity.

To understand the stereorecognition ability brought about by the spiro phosphite ligands in the catalysts, a suitable

crystal [Rh(COD((*S*)-**1a**)$_2$)]BF$_4$ was grown. The X-ray analysis of the crystal structure showed that two coordinating spiro phosphite ligands created an effective asymmetric environment around the rhodium (Figure 2).[8] Two phenyl groups of the phosphite ligands blocked one side of the complex, and both arylboronic acid and aldehyde could not access and coordinate with rhodium from the back. A stereorecognition model was proposed in Scheme 1 to

Scheme 1. Stereorecognition Model for the Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids to Aldehydes
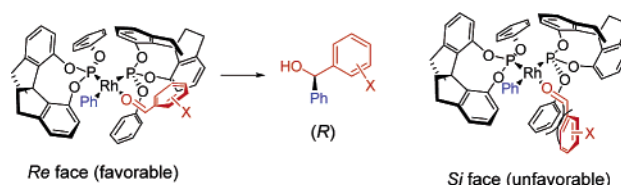
rationalize the absolute configuration of the products in the addition of arylboronic acids to aldehydes. It can be seen from the model that the transfer of the phenyl group to the *Re* face of aldehyde is much more favorable.

In summary, highly efficient rhodium-catalyzed asymmetric addition of arylboronic acids to aldehydes has been realized by using chiral spiro phosphite ligands, affording diarylmethanols in excellent yields and good enantiomeric excesses. The high activity and enantioselectivity of rhodium complexes of chiral spiro monophosphites for the addition of arylboronic acids to aldehydes indicated a potential for wide application of these ligands in asymmetric transition-metal-catalyzed carbon−carbon bond forming reactions.

Supporting Information Available: Experimental procedures, the characterizations of ligands and products, and the analysis of ee values of addition products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) See Supporting Information for ligand syntheses.

(8) See Supporting Information for the crystal data and structure refinement of [Rh(COD)((*S*)-**1a**)$_2$]BF$_4$.