Enantioselective Rh-Catalyzed Addition of Arylboronic Acids to *N*-Tosylarylimines

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Abstract: A highly enantioselective rhodium-catalyzed addition of arylboronic acids to *N*-tosylarylimines is described, using chiral binaphtholic phosphite and phosphoramidite ligands. The best ee values (76–99%), associated with moderate to good chemical yields, were obtained with binaphtholic phosphoramidite ligands containing a bulky chiral amine.

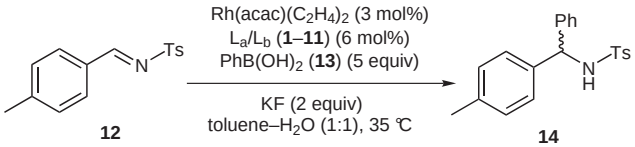
Key words: arylations, arylboronic acids, asymmetric catalysis, imines, rhodium

Enantiopure diarylmethylamines represent an interesting synthetic target due to the presence of this substructure in a variety of pharmacologically active compounds.[1] In recent years, considerable progress has been achieved in the catalytic enantioselective arylation of imines as an effective methodology for the synthesis of these important substrates.[2] Excellent enantioselectivities have been reported for the addition of arylzinc,[2] aryltin[3] and aryltitanium[4] reagents. More recently, arylboron reagents have received increasing attention because of their availability, stability, low toxicity, and compatibility with a wide range of functional groups.[5] So far, only a few reports have been published on the rhodium(I)-catalyzed asymmetric addition of arylboron reagents to imines. Tomioka and co-workers described the first enantioselective addition of arylboronic acids and arylboroxines to *N*-tosylarylimines using a chiral amidophosphane ligand.[6] Enantiomeric ratios above 95:5 were obtained through steric tuning of both the imine and the boron reagent. Hayashi and co-workers reported excellent enantioselectivities for the addition of arylboroxines to *N*-tosyl- and *N*-nosylarylimines employing chiral diene ligands.[7] Ellman and co-workers reported an example of high enantioselectivity in the addition of arylboronic acids to *N*-diphenylphosphinoylarylimines using deguphos as chiral ligand.[8] More recently, monodentate phosphite ligands have been used by Zhou and co-workers in the highly enantioselective (85–96% ee) addition of arylboronic acids to *N*-tosylarylimines,[9] while the group of de Vries, Feringa and Minnaard reported good enantioselectivities (82–94% ee) in the rhodium-catalyzed arylation of *N*,*N*-dimethylsulfamoylarylimines, using monodentate phosphoramidite ligands.[10]

In our laboratories, a number of chiral tropos phosphorus ligands, based on a flexible biphenol unit and a chiral P-bound alcohol (phosphites) or secondary amine (phosphoramidites), were recently synthesized and used (individually or as a binary mixture) in the Rh-catalyzed asymmetric hydrogenation of functionalized olefins,[11] and in the Rh-catalyzed conjugate addition of aryl boronic acids to enones and enoates.[12]

In this letter, we report our findings in the rhodium-catalyzed enantioselective addition of arylboronic acids to *N*-tosylarylimines, using monodentate biphenolic and binaphtholic phosphites and phosphoramidites as chiral ligands.

A small library[13] of chiral biphenolic and binaphtholic phosphites and phosphoramidites (**1**–**11**, Figure 1)[14] was initially screened in the Rh-catalyzed addition of phenylboronic acid to *N*-tosyl-*p*-tolylaldehyde imine, using the conditions reported by Zhou and co-workers[9] (Scheme 1). The ligands were tested either individually (Table 1, entries 1–11) or as binary combinations (L_a/L_b 1:1, 3 mol% each)[11,12] (Table 1, entries 12–16).



Scheme 1 Enantioselective addition of phenylboronic acid to *N*-tosyl-*p*-tolylaldehyde imine: preliminary screening (see Table 1)

In general, phosphoramidites were more selective than phosphites: good enantiomeric excesses were obtained with binaphtholic phosphoramidite ligands containing a bulky chiral amine (i.e. ligands **9** and **11**; entries 9 and 11). Unfortunately, the yields were only moderate for most of the ligands (good yields were obtained with the binaphtholic phosphite **7** and Monophos® (**8**), entries 7 and 8). When binaphtholic phosphite **7** [yield: 87%, ee: 40% (*S*); entry 7] and Monophos® (**8**) [yield: 90%, ee: 27% (*S*); entry 8] were used in combination, a small cooperative effect was observed [yield: 95%, ee: 50% (*S*); entry 12]. Although the increase of ee obtained by the combination

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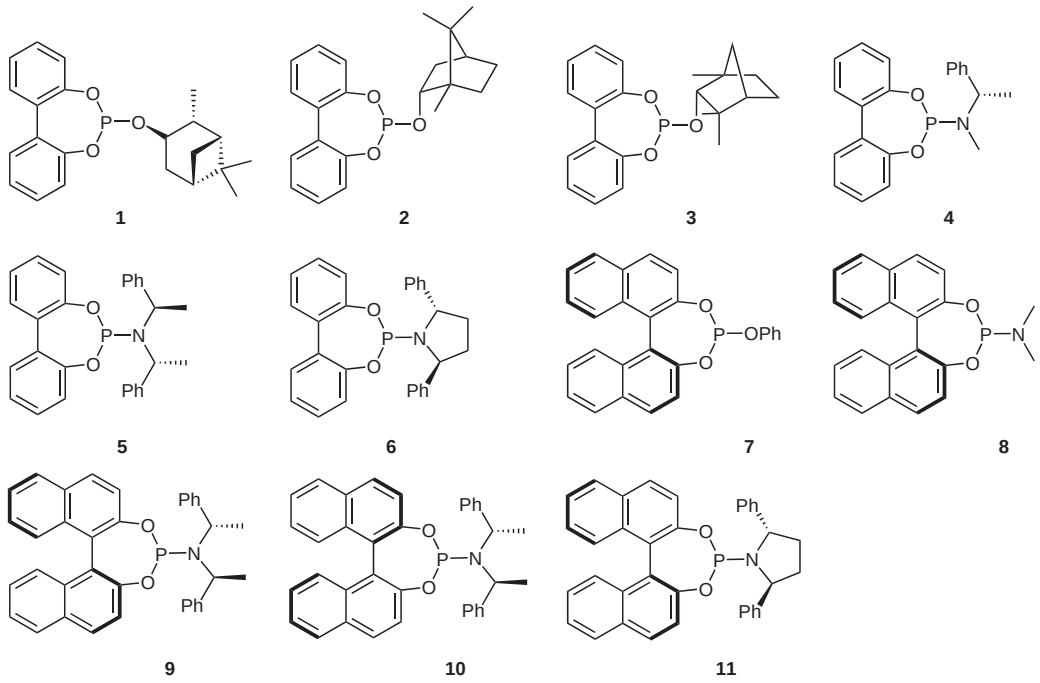


Figure 1 Library of chiral biphenolic and binaphtholic phosphite and phosphoramidite ligands

Table 1 Screening of Ligands **1**–**11** and of Some Ligand Binary Mixtures in the Addition of Phenylboronic Acid to *N*-Tosyl-*p*-tolylaldehyde Imine[a]

Entry	L_a	L_b	Conversion[b] (%)	ee[c] (%)
1	**1**	–	42	3 (*R*)
2	**2**	–	79	8 (*S*)
3	**3**	–	19	7 (*S*)
4	**4**	–	50	23 (*S*)
5	**5**	–	33	22 (*R*)
6	**6**	–	61	80 (*S*)
7	**7**	–	87	40 (*S*)
8	**8**	–	90	27 (*S*)
9	**9**	–	45	90 (*S*)
10	**10**	–	0	–
11	**11**	–	25	93 (*S*)
12	**7**	**8**	95	50 (*S*)
13	**7**	**9**	17	49 (*S*)
14	**9**	**1**	50	61 (*S*)
15	**7**	**4**	56	0
16	**8**	**6**	55	24 (*S*)

[a] Reaction conditions: phenylboronic acid (5 equiv), *N*-tosyl-*p*-tolylaldehyde imine (1 equiv), $Rh(acac)(C_2H_4)_2$ (3 mol%), L (6 mol%), toluene–H_2O (1:1) with KF (2 equiv), 35 °C, 24 h.
[b] Calculated by ^1H NMR analysis of the crude reaction mixture.
[c] Both the ee values and the absolute configurations were determined by HPLC using a Chiralcel OD-H column (see ref. 9).

of these two ligands is only marginal and not synthetically useful, it implies that both ligands are present in the rhodium complex during the enantiodiscriminating step of the reaction.

Encouraged by the ee values obtained with ligands **9** and **11**, we decided to screen different reaction conditions (solvent, base and temperature) using ligand **9**, in order to improve the yields of the reaction. While no improvement was observed using numerous solvent–base combinations [anhyd toluene, acetone, THF–H_2O (1:1), dioxane–H_2O (10:1), dioxane–H_2O (1:2) as solvents, with LiF, KF, KOH, Et_3N as bases], good yields and ee values were finally obtained using anhydrous dioxane with LiF as base.[15]

A small sublibrary of phosphoramidite ligands was then tested under these optimized conditions in the addition of phenylboronic acid to *N*-tosyl-*p*-tolylaldehyde imine, including also ligand **15** (the diastereomer of **11**) and binaphtholic phosphoramidite **16** derived from bis(1-naphthylethyl)amine (Figure 2 and Table 2).

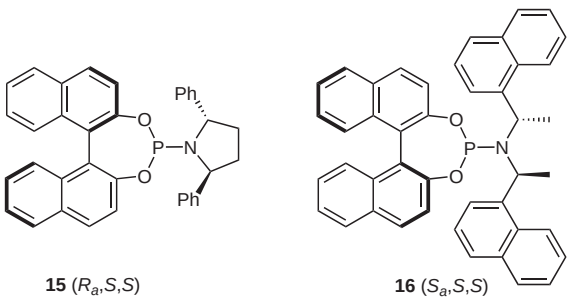


Figure 2 Structure of ligands **15** and **16** used in the screening under optimized reaction conditions

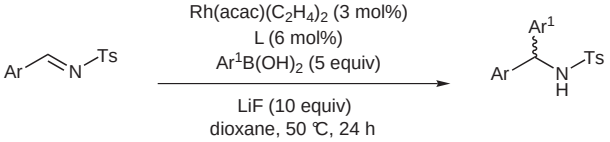
Table 2 Addition of Phenylboronic Acid to *N*-Tosyl-*p*-tolylaldehyde Imine[a]

Entry	L	Conversion[b] (%)	ee[c] (%)
1	**9**	60	87 (*S*)
2	**10**	21	33 (*R*)
3	**11**	93	90 (*S*)
4	**15**	82	86 (*S*)
5	**6**	65	84 (*S*)
6	**16**	15	76 (*R*)

[a] Reaction conditions: phenylboronic acid (5 equiv), *N*-tosyl-*p*-tolylaldehyde imine (1 equiv), $Rh(acac)_2(C_2H_4)$ (3 mol%), L (6 mol%), anhyd dioxane with LiF (10 equiv), 50 °C, 24 h.
[b] Calculated by ^1H NMR analysis of the crude reaction mixture.
[c] Both the ee values and the absolute configurations were determined by HPLC using a Chiralcel OD-H column (see ref. 9).

A clear matched combination of the binaphthol chiral axis and of the amine stereocenters is observed for phosphoramidite **9** (S_a,*S*,*S*) [yield: 60%, ee: 87% (*S*); entry 1] with respect to **10** (R_a,*S*,*S*) [yield: 21%, ee: 33% (*R*); entry 2]. On the contrary, in the case of **11** (S_a,*S*,*S*) and **15** (R_a,*S*,*S*), which also share the same enantiomer of the amine moiety, the opposite enantiomer of the binaphthol chiral axis plays only a very marginal role [ee: 90% (*S*) vs. ee: 86% (*S*), entries 3 and 4]. The importance of the 2,5-diphenylpyrrolidine moiety is further confirmed by the 84% ee in favor of the *S*-enantiomer (entry 5) obtained using ligand **6**, which is devoid of the chiral axis. Ligands **11** and **6** have already been used by us[11,12] and others[16] as very effective ligands in different reaction processes. Ligand **16** (S_a,*S*,*S*),[17] which contains a bulkier amine substituent, showed a reduced yield and a reversed enantiofacial selectivity [yield: 15%, ee: 76% (*R*); entry 6]. This result might indicate that a different mechanism is operating in this case: possibly the active Rh complex contains only one ligand.

Having established the optimal synthetic protocol, the scope of this arylation reaction was examined, testing several aromatic imines and arylboronic acids, and using our best ligands **9** and **11** (Scheme 2 and Table 3).



Scheme 2 Asymmetric arylation of *N*-tosylarylimines with arylboronic acids: scope of the reaction

Table 3 Asymmetric Arylation of *N*-Tosylarylimines with Arylboronic Acids:[18] Scope of the Reaction

Entry	Ar	Ar[1]	L	Conversion[a] (%)	ee[b] (%)
1	2-MeC_6H_4	Ph	**9**	54	78 (*S*)
2	2-MeC_6H_4	Ph	**11**	42	71 (*S*)
3	4-$OMeC_6H_4$	Ph	**9**	40	89 (*S*)
4	4-$OMeC_6H_4$	Ph	**11**	70	81 (*S*)
5	1-naphthyl	Ph	**9**	40	99 (*S*)
6	1-naphthyl	Ph	**11**	32	51 (*S*)
7	4-BrC_6H_4	Ph	**9**	16	89 (*S*)
8	4-BrC_6H_4	Ph	**11**	30	87 (*S*)
9	Ph	4-MeC_6H_4	**9**	88	87 (*R*)
10	Ph	4-MeC_6H_4	**11**	80	87 (*R*)
11	Ph	4-$OMeC_6H_4$	**9**	60	68 (*R*)
12	Ph	4-$OMeC_6H_4$	**11**	85	76 (*R*)

[a] Calculated by ^1H NMR analysis of the crude reaction mixture.
[b] Both the ee values and the absolute configurations were determined by HPLC using a Chiralcel OD-H column (see ref. 9).

Good to excellent ee values (76–99%) were obtained in the arylation of differently substituted *N*-tosylarylimines, containing either electron-donating or electron-withdrawing substituents, while the catalytic efficiency was moderate in most cases, as witnessed by the conversions. An excellent ee (99%; entry 5) was obtained with *N*-tosyl-1-naphthaldehyde imine using ligand **9**, while only a moderate enantioselectivity (ee: 51%; entry 6) was observed with ligand **11**. Electron-rich substrates gave generally higher yields (entries 1–4), while a slower addition reaction, associated with lower overall yields, occurred with electron-poor substrates (entries 7 and 8). Electron-rich arylboronic acids (entries 9–12) gave generally good yields in the addition to *N*-tosylbenzaldimine, associated with moderate to good ee values.

Diarylmethylamines can be obtained from their *N*-tosyl derivatives by removal of the *N*-tosyl group, in high yields and without loss of enantiomeric purity, by reaction with SmI_2.[19]

In summary, we have described a highly enantioselective arylation of *N*-tosylarylimines with arylboronic acids catalyzed by rhodium complexes of chiral bulky binaphtholic phosphoramidite ligands. In particular, ligand **9**, which gave high ee values and reasonable yields, can be easily prepared from commercially available starting materials. We are currently exploring the applicability of this procedure to differently protected/activated arylimines (with more easily cleavable activating/protecting groups) and to ketimines.

Acknowledgment

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(18) **General Procedure for the Arylation of *N*-Tosylarylimines**: In a flame-dried Schlenk tube flushed with nitrogen, $Rh(acac)(C_2H_4)_2$ (1.2 mg, 4.65 μmol, 3 mol%) and the ligand (9.30 μmol, 6 mol%) were dissolved in anhyd dioxane (0.75 mL). After stirring for 30 min at r.t., LiF (1.5 mmol) and the substrate (0.15 mmol) were added followed by the appropriate arylboronic acid (0.75 mmol). The resulting mixture was stirred at 50 °C for 24 h, quenched with H_2O (3 mL) and extracted with CH_2Cl_2 (3 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under vacuum. The residue was purified by flash chromatography on silica gel (*n*-hexane–EtOAc, 7:3) affording the *N*-tosyldiarylmethylamine as a white solid.

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