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Enantioselective Rh-Catalyzed Arylation of *N*-Tosylarylimines with Arylboronic Acids

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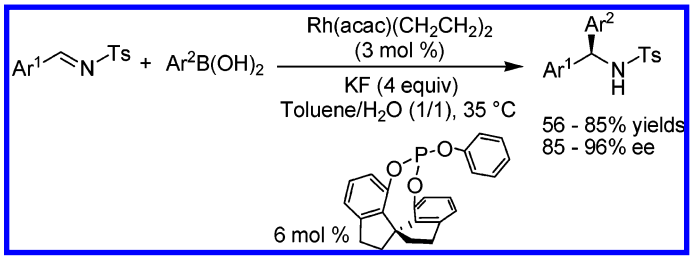
ABSTRACT



The asymmetric arylation of *N*-tosylarylimines with arylboronic acids was realized by using rhodium/(*S*)-ShiP as catalyst. The reaction proceeded in aqueous toluene to give diarylmethylamines in good yields with up to 96% ee.

The addition of organometallic reagents to imines represents an attractive area in current organic synthesis. The catalytic enantioselective version of this reaction provides a particularly useful access to chiral amines,[1] which are synthetically important chiral building blocks for pharmaceutically active compounds.[2] In recent years, considerable efforts have been made and great progress has been achieved in the catalytic enantioselective arylation of imines. Bräse and co-workers reported the addition of diphenylzinc to *N*-formylimines employing chiral ketimine catalysts.[3] Transformations of arylstannanes,[4] aryltitaniums,[5] and arylboroxines[6] to *N*-sulfonylimines mediated by rhodium complexes were developed by Hayashi and Tomioka by using monophosphines, bisphosphines, amidophosphanes, and chiral dienes as chiral ligands, giving *N*-tosyldiarylmethylamides in excellent ee values. Nevertheless, the requirement for the use of toxic, moisture-sensitive, or noncommercially available organometallic reagents and sometimes the need for sterically tuned substrates for high enantioselectivity may limit their application. Thus, the development of an efficient and general method for the synthesis of optically active diarylmethylamines is still highly desirable.

Absent from these organometallic reagents, however, are the arylboronic acids, which are attractive compounds due to their low cost, low toxicity, stability toward air and moisture, and tolerance to a variety of functional groups. The arylboronic acids can be transformed to various electrophiles in the presence of Rh(I) complex as catalyst.[7] However, their

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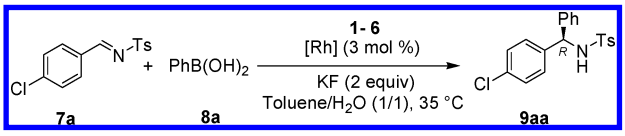
application in the asymmetric addition to imines is rare.[8] The only example of catalytic asymmetric addition of arylboronic acids to *N*-diphenylphosphinoylbenzaldimine was reported by Ellman for a limited set of substrates.[8a,9] Recently, we reported that the rhodium complexes with spiro monophosphite ligands were efficient catalysts for the asymmetric addition of arylboronic acids to aromatic aldehydes, producing diarylmethanols in high ee values.[10] Herein, we wish to present the highly enantioselective addition of arylboronic acids to *N*-tosylarylimines catalyzed by Rh complexes with a spiro monophosphite ligand (*S*)-ShiP. This investigation expands the scope of application of arylboronic acids as aryl sources and provides a practical entry to the synthesis of optically active diarylmethylamines.

We began our experiment under the identical conditions used in our previous study of rhodium-catalyzed addition of phenylboronic acid to aldehydes.[10] The reaction of phenylboronic acid and *N*-tosyl-4-chlorobenzaldehyde imine **7a** was performed in aqueous toluene at 35 °C using [RhCl(CH$_2$CH$_2$)]$_2$ (3 mol % of Rh) as a precatalyst and (*S*)-ShiP as a chiral ligand. The addition product **9aa** was gratifyingly obtained in 70% yield with 89% ee after 20 h (Table 1, entry 1). Hydrolysis of imine was the main side reaction, which became substantial when the reaction was carried out in solvents other than toluene.[11] Other Rh(I) compounds as precursors were also investigated with ligand **1** (entries 2−6). The use of cationic [Rh(COD)(MeCN)$_2$]BF$_4$ under the same conditions gave a comparable yield (72%) but a lower enantioselectivity (19%). The Rh(acac)(C$_2$H$_4$)$_2$ emerged as the best choice of catalyst precursors, affording the addition product in good yield (77%) and high ee (93%).

Table 1. Optimization of the Reaction Conditions



entry	[Rh]	ligand	yield[a] (%)	ee[b] (%)
1	[RhCl(C$_2$H$_4$)$_2$]$_2$	**1**	75	89
2	[Rh(COD)(MeCN)$_2$]BF$_4$	**1**	72	19
3	Rh(COD)$_2$BF$_4$	**1**	43	49
4	[Rh(COD)$_2$Cl]$_2$	**1**	56	48
5	Rh(acac)(CO)$_2$	**1**	70	81
6	Rh(acac)(C$_2$H$_4$)$_2$	**1**	77	93
7	Rh(acac)(C$_2$H$_4$)$_2$	**2**	69	83
8	Rh(acac)(C$_2$H$_4$)$_2$	**3**	58	62
9	Rh(acac)(C$_2$H$_4$)$_2$	**4**	63	84
10	Rh(acac)(C$_2$H$_4$)$_2$	**5**	30	13
11	Rh(acac)(C$_2$H$_4$)$_2$	**6**	9	10
12	Rh(acac)(C$_2$H$_4$)$_2$	**1**	25	88
13[c]	Rh(acac)(C$_2$H$_4$)$_2$	**1**	85	93 (99)[d]

[a] Isolated yield after chromatography. [b] Determined by chiral HPLC using a Chiralcel OD column. [c] With 4 equiv of KF. [d] After a simple recrystallization.

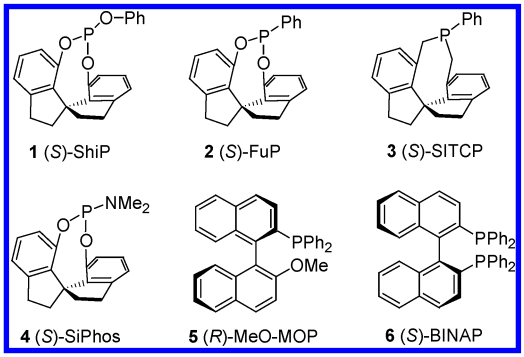


Figure 1. Tested chiral ligand.

Encouraged by this result, we tested different chiral ligands shown in Figure 1. The monodentate ligands **2**−**4** containing a spirobiindane scaffold gave the desired product **9aa** in 58−69% yields with 62−84% ee (Table 1, entries 7−9), though these were lower than those obtained with ligand **1**. However, the binaphthol-based ligands **5** (MeO-MOP) and **6** (BINAP) were found to be less efficient in this reaction in terms of either reactivity or enantioselectivity (entries 10 and 11). These results indicated that the spiro monodentate ligands having a large dihedral angle backbone, especially (*S*)-ShiP, were crucial for efficient control of enantioselectivity in the Rh-catalyzed addition of arylboronic acids to imines. The use of KF as an additive is important for achieving high yield. For example, the reaction in the absence of KF gave only 25% of the addition product, while the reactions with 2 or 4 equiv of KF provided the addition product in 77% and 85% yield, respectively (entries 6 and 13).

Having established an optimal protocol, the arylation of a variety of aromatic imines was examined (Scheme 1) with 3 mol % of Rh(acac)(C$_2$H$_4$)$_2$/(*S*)-ShiP catalyst at 35 °C in aqueous toluene. The results are summarized in Table 2. Interestingly, the imines bearing both electron-donating and -withdrawing groups are tolerated in the arylation reaction with arylboronic acids. Furthermore, the positions of substituents of imine substrates is not restrictive for obtaining high enantioselectivites, as the phenylations of para-, meta-, and ortho-subsitituted arylimines were all successful to give the desired products in 92−96% ee (Table 2, entries 1−10). 1-Naphthaldehyde imine **7k** and 2-furaldehyde imine **7l** can also react with phenylboronic acid to produce the corresponding addition products in 76% yield with 96% ee and

(7) For rhodium-catalyzed addition of arylboronic acids to aldehydes, imines and α,β-unsaturated compounds, see reviews: (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

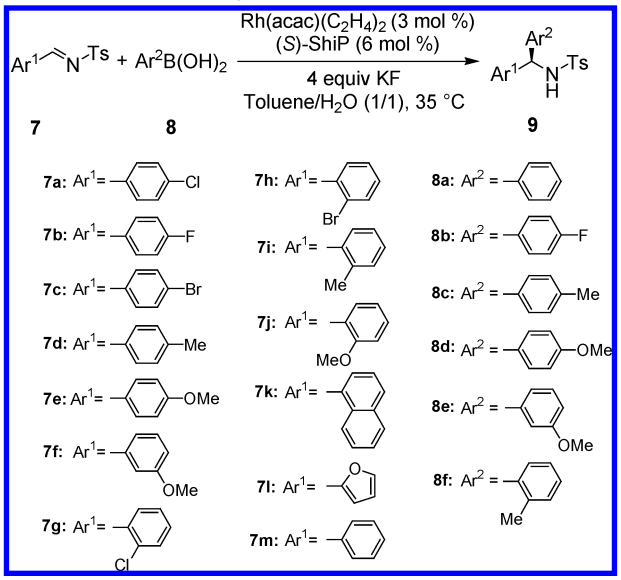
(8) For the diastereoselective addition of arylboronic acids to chiral sulfinimines, see: (a) Weix, D. J.; Shi, Y.-L.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092. (b) Bolshan, Y.; Batey, R. A. *Org. Lett.* **2005**, *7*, 1481.

(9) When this manuscript was submmited, a related publication by Feringa and Minnaard on the addition of arylboronic acids to *N*-sulfamonyl aldimines using phosphoramidite ligands appeared on the Internet: Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789.

(10) Duan, H.-F.; Xie, J.-H.; Shi, W.-J.; Zhang, Q.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1479.

(11) The reactions in aqueous ClCH$_2$CH$_2$Cl, MeOCH$_2$CH$_2$OMe, THF, dioxane, and *i*-PrOH all gave the isolated yield of **9aa** below 40%.

Scheme 1. Asymmetric Arylation of Imines **7** with Arylboronic Acids **8**



84% yield with 85% ee, respectively (entries 11 and 12). A highly asymmetric induction was also observed in the addition of a variety of arylboronic acids to benzaldehyde imine **7m** (entries 13−17). The corresponding *N*-tosyldiarylmethylamides with reverse configuration were achieved with excellent enantiomeric excesses (91−95%), even as the electron-deficient 4-fluorophenylboronic acid was used as nucleophile.

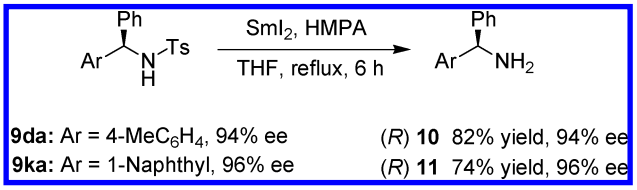
The chiral diarylmethylamines can be obtained by deprotection of the *N*-tosyl group on the arylation products using samarium(II) iodide under standard conditions (Scheme 2).

Table 2. Asymmetric Arylation of Imines **7** with Arylboronic Acids **8**[a]

entry	Ar^1	Ar^2	yield[b] (%)	ee[c] (%)
1	**7a**	**8a**	85 (**9aa**)	93 (*R*)
2	**7b**	**8a**	80 (**9ba**)	93 (*R*)
3	**7c**	**8a**	82 (**9ca**)	93 (*R*)
4	**7d**	**8a**	77 (**9da**)	94 (*R*)
5	**7e**	**8a**	65 (**9ea**)	93 (*R*)
6	**7f**	**8a**	72 (**9fa**)	96 (*R*)
7	**7g**	**8a**	79 (**9ga**)	95 (*R*)
8	**7h**	**8a**	76 (**9ha**)	93 (*R*)
9	**7i**	**8a**	73 (**9ia**)	95 (*R*)
10	**7j**	**8a**	67 (**9ja**)	92 (*R*)
11	**7k**	**8a**	76 (**9ka**)	96 (*R*)
12	**7l**	**8a**	84 (**9la**)	85 (*R*)
13	**7m**	**8b**	56 (**9mb**)	94 (*S*)
14	**7m**	**8c**	75 (**9mc**)	92 (*S*)
15	**7m**	**8d**	70 (**9md**)	95 (*S*)
16	**7m**	**8e**	68 (**9me**)	91 (*S*)
17	**7m**	**8f**	65 (**9mf**)	93 (*S*)

[a] Reaction conditions: **7**/**8**/KF/[Rh]/(*S*)-ShiP = 1:2:4:0.03:0.06 (mmol); toluene/H_2O (1:1, 2 mL) at 35 °C for 20 h. [b] Isolated yield. [c] Determined by chiral HPLC (Supporting Information).

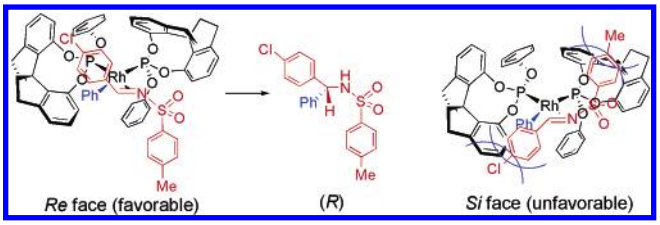
Scheme 2. Deprotection of *N*-Tosyldiarylmethylamides



Thus, **9da** or **9ka** were treated with SmI_2 in refluxing THF−HMPA for 6 h to give free amines **10** or **11** in good yield without loss of their enantiomeric purities.

A stereorecognition model for understanding the pathway of the transformation of phenyl to imine was proposed based on the crystal structure of catalyst $[Rh(\mathbf{1})_2(COD)]^+$.[12] From Scheme 3, we can see that the (*S*)-ShiP ligands created an

Scheme 3. Stereorecognition Model for the Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids to Imine



efficient chiral environment around the rhodium atom. *N*-Tosyl-4-chlorobenzaldehyde imine favorably coordinated to the Rh atom on the *Re* face, and the phenyl group transformed to the imine from its *Re* face, providing the addition product with *R* configuration. In contrast, the coordination of imine to Rh on the *Si* face was very unfavorable due to the repulsions of the 4-chlorophenyl and tosyl groups of the imine substrate with the backbone of the ligand.

In conclusion, we have developed an efficient catalyst, rhodium complex of monodentate spiro phosphite (*S*)-ShiP for asymmetric arylation of *N*-tosylarylimines using arylboronic acids. This highly enantioselective method provided a facile access to a variety of optically active diarylmethylamine derivatives. Further application of this rhodium/phosphite catalyst in other C−C bond-forming reactions is in progress in our group.

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Supporting Information Available: Experimental procedures, characterization, and analysis of ee values of arylation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See the Supporting Information for details.