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# *N*-Boc-L-Valine-Connected Amidomonophosphane Rhodium(I) Catalyst for Asymmetric Arylation of *N*-Tosylarylimines with Arylboroxines

Masami Kuriyama, Takahiro Soeta, Xinyu Hao, Qian Chen, and Kiyoshi Tomioka*

*Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan*

Received April 28, 2004; E-mail: tomioka@pharm.kyoto-u.ac.jp

The asymmetric synthesis of diarylmethylamines is very important because these amines are subunits of some biologically significant compounds.[1] However, the efficient asymmetric synthesis of these amines is rather limited.[2−4] Despite many reports, only two examples of the catalytic asymmetric additions of arylmetallic reagents to arylimine derivatives have been reported.[5] Hayashi developed a chiral MOP-based phosphane rhodium(I)-catalyzed addition of arylstannanes to *N*-sulfonylimines.[6] A diphenylzinc addition to masked *N*-formylimines employing a paracyclophane-based ketimine catalyst was reported by Bräse.[7] From the viewpoint of green chemistry, however, the catalytic asymmetric reaction of imines with less toxic arylation reagents is desirable.[8,9] We selected arylboron reagents[10] as an aryl source and succeeded in the development of the efficient asymmetric arylation of imines. The key points to the success were (1) L-valine-connected amidomonophosphane as a chiral ligand to rhodium(I), (2) steric tuning of arylimines, and (3) arylboroxines instead of arylboronic acids.

We started our arylation approach with hemilabile chiral amidomonophosphanes **1** and **2** (Figure 1), which were proven to be effective in two different types of asymmetric addition reactions. The less bulky phosphane **1**-rhodium(I) catalyzes the conjugate addition of arylboronic acids to enones,[11] and the more bulky **2**-copper(I) mediates the 1,2-addition of dialkylzinc reagents to alkyl- and arylimines.[12] Unfortunately, both phosphanes were ineffective in the asymmetric rhodium(I)-catalyzed arylation of 4-tolylaldehyde *N*-toluenesulfonylimine **8a** with phenylboronic acid **9** at 100 °C for 1 h in dioxane, giving *N*-tosyl-diarylmethylamide **10a** in marginal stereoselectivity (Scheme 1; Table 1, entries 1 and 2). BINAP was also not the good ligand, giving **10a** with 67:33 er (entry 3).

The replacement of the pivaloyl group of **1** and **2** by a readily available chiral α-amino acid is the advantage of the phosphane scaffold. Although *N*-Boc-D- and L-valine-connected bulky amidophosphanes **4** and **5** were less effective, giving **10a** with 53:47 er and 62:38 er in low chemical yields, less bulky **6** and **7** gave better reactivity (over 90% yield within 1 h) and selectivity (70:30 er and 76:24 er (entries 4−7)).

Encouraged by the enantioselectivity improvement with **7**, we then turned our attention to the steric tuning of the imine. Enantioselectivity was found to be dependent on the position of a substituent on the phenyl ring. Tolylaldehyde imines **8b** and **8c** bearing 3- and 2-methyl substituents were converted to **10b** and **10c** using 3 mol % of **7**-Rh(I) catalysis with better 78:22 er and 87:13 er (entries 8 and 9). Since a trimethylsilyl (TMS) group on a phenyl ring is easily convertible to a proton or halogen, the arylation was examined with 2-TMS-benzaldehyde[13] imine **8d**. The enantioselectivity was improved to 89:11 er to give **10d** (entry 10).

The **7**-Rh(I)-catalyzed arylation of **8d** with phenylboronic acid **9** in dioxane, THF, and *n*-PrOH at 60 °C gave **10d** with the same 90:10 er in 8, 20, and 72% yields (entry 11). The chemical yield

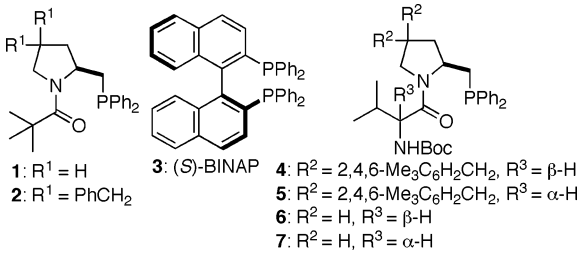


***Figure 1.*** Chiral phosphane ligands **1**−**7**.

***Scheme 1.*** Asymmetric Arylation of *N*-Tosylarylimine **8** with Phenylboron **9** and **11a**, Giving **10**

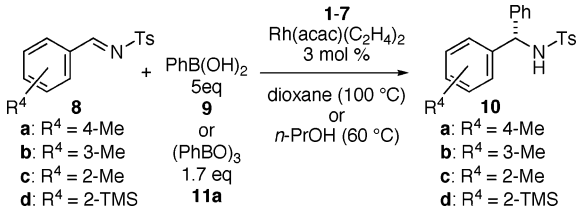


***Table 1.*** Asymmetric Arylation of *N*-Tosylarylimine **8** with Phenylboron **9** and **11a** Catalyzed by **1**−**7** and Rhodium(I)

| entry | imine **8** | $R^4$ | **1**–**7** | boron | solvent | yield (%) | er[a] |
|---|---|---|---|---|---|---|---|
| 1 | **8a** | 4-Me | **1** | **9** | dioxane | 80 | 51:49 |
| 2 | **8a** | 4-Me | **2** | **9** | dioxane | 20 | 53:47 |
| 3 | **8a** | 4-Me | **3** | **9** | dioxane | 88 | 67:33 |
| 4 | **8a** | 4-Me | **4** | **9** | dioxane | 26 | 53:47 |
| 5 | **8a** | 4-Me | **5** | **9** | dioxane | 24 | 62:38 |
| 6 | **8a** | 4-Me | **6** | **9** | dioxane | 91 | 70:30 |
| 7 | **8a** | 4-Me | **7** | **9** | dioxane | 95 | 76:24 |
| 8 | **8b** | 3-Me | **7** | **9** | dioxane | 99 | 78:22 |
| 9 | **8c** | 2-Me | **7** | **9** | dioxane | 99 | 87:13 |
| 10 | **8d** | 2-TMS | **7** | **9** | dioxane | 91 | 89:11 |
| 11 | **8d** | 2-TMS | **7** | **9** | *n*-PrOH | 72 | 90:10 |
| 12 | **8d** | 2-TMS | **7** | **11a** | *n*-PrOH | 95 | 90:10 |

[a] Determined by HPLC (Supporting Information).

of **10d** with 90:10 er was improved to 95% by using phenylboroxine ($(PhBO)_3$) **11a** in *n*-PrOH at 60 °C for 3 h (entry 12).

It was an unexpected pleasure to find that the arylation of **8d** with substituted phenylboroxines **11b**−**11f** gave **10** with higher enantioselectivity up to 97:3 (Scheme 2). For example, 3-chlorophenylation of **8d** with **11f** gave **10df**[14] with 97:3 er quantitatively (Table 2, entry 9). The electron-donating 3-methoxyphenyl group was introduced to **8d** with **11e**, giving **10de** with 95:5 er in 87% yield (entry 8). 4-Methoxy- and 4-chlorophenyl groups were also introduced to **8d** with **11c** and **11d**, giving **10dc** and **10dd** with 94:6 er (84%) and 95:5 er (97%) (entries 6 and 7). 4-Phenylphenylboroxine **11b** was also a good donor to give **10db** with 96:4 er in 98% yield (entry 4).

Other than 2-TMS-phenylimine **8d**, 2-, 3-, and 4-tolylimines **8a**−**8c** were converted, upon treatment with 4-phenylphenylboroxine



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***Scheme 2.*** Asymmetric Arylation of **8** with **11**, Giving **10**

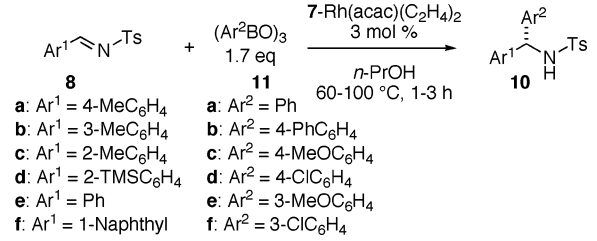
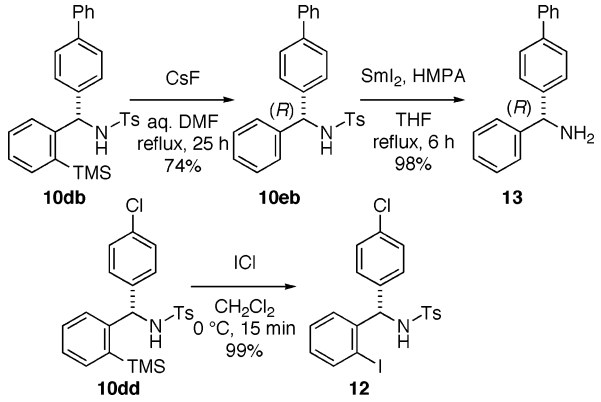



***Table 2.*** Rhodium(I)-**7**-Catalyzed Asymmetric Arylation of *N*-Tosylarylimines **8** with Arylboroxines **11** in *n*-PrOH, Giving **10**

| entry | 8 | $Ar^1$ | 11 | $Ar^2$ | temp (°C) | yield (%) | er[a] |
|---|---|---|---|---|---|---|---|
| 1 | **8a** | 4-$MeC_6H_4$ | **11b** | 4-$PhC_6H_4$ | 60 | 86 | 86:14 |
| 2 | **8b** | 3-$MeC_6H_4$ | **11b** | 4-$PhC_6H_4$ | 60 | 90 | 88:12 |
| 3 | **8c** | 2-$MeC_6H_4$ | **11b** | 4-$PhC_6H_4$ | 60 | 97 | 93:7 |
| 4 | **8d** | 2-$TMSC_6H_4$ | **11b** | 4-$PhC_6H_4$ | 60 | 98 | 96:4 |
| 5 | **8e** | Ph | **11b** | 4-$PhC_6H_4$ | 60 | 83 | 83:17 |
| 6 | **8d** | 2-$TMSC_6H_4$ | **11c** | 4-$MeOC_6H_4$ | 80 | 84 | 94:6 |
| 7 | **8d** | 2-$TMSC_6H_4$ | **11d** | 4-$ClC_6H_4$ | 80 | 97 | 95:5 |
| 8 | **8d** | 2-$TMSC_6H_4$ | **11e** | 3-$MeOC_6H_4$ | 60 | 87 | 95:5 |
| 9 | **8d** | 2-$TMSC_6H_4$ | **11f** | 3-$ClC_6H_4$ | 60 | 99 | 97:3 |
| 10 | **8f** | 1-Naphthyl | **11b** | 4-$PhC_6H_4$ | 100 | 88 | 96:4 |

[a] Determined by HPLC or NMR (Supporting Information).

***Scheme 3.*** Protodesilylation, Iododesilylation, and Detosylation




**11b**, to the corresponding diarylmethylamides **10** with 93:7 er, 88:12 er, and 86:14 er (entries 1−3). Naphthylimine **8f** was also a good acceptor with **11b**, being converted to **10fb** with 96:4 er in 88% yield (entry 10).

The 2-TMS group on the phenyl ring of the product was easily convertible to other functional groups (Scheme 3). Thus, **10db** was protodesilylated with cesium fluoride in refluxing aqueous DMF for 25 h to afford (*R*)-**10eb**[15] in 74% yield without any racemization. This arylation of the TMS-modified imine-protodesilylation sequence is complementary to the less effective arylation of phenylimine **8e** (Table 2, entries 4 vs 5). Iododesilylation of **10dd** with iodine chloride in methylene chloride at 0 °C for 15 min gave 2-iodo derivative **12**, a useful starting material suitable for the Suzuki−Miyaura coupling, quantitatively without any racemization. Treatment of **10eb** with samarium iodide in refluxing THF−HMPA for 6 h gave the corresponding detosylated (*R*)-**13**[16] in 98% yield without any loss of optical purity. The *si*-face attack to **8** in the arylation was determined from the established absolute configuration of **10eb** and **13**.[16]

In conclusion, a catalytic asymmetric arylation of sterically tuned imines with arylboroxines was developed by using *N*-Boc-L-valine-connected amidomonophosphane rhodium(I) catalyst in *n*-PrOH. It is also important to note that further modification of the amidophosphane is possible with use of other natural α-amino acids. The TMS group used for the steric tuning of the imine is convertible to other functionalities that are applicable as a key foothold for the carbon−carbon bond forming coupling reactions.

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**Supporting Information Available:** Experimental procedure, characterization data, NMR spectra, and HPLC traces (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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