DOI: 10.1002/ejoc.200901139

Catalytic Enantioselective Addition of Phenylboronic Acid and Phenylboroxine to *N*-Tosylimines: Pd^{II} and Rh^{I} Catalysis

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Keywords: *N*-Tosylarylimines / Phenylboronic acid / Addition / Chiral amines / Enantioselective catalysis

This is the first account of a successful, Pd^{II}-catalysed enantioselective addition of phenylboronic acid to electron-deficient *N*-tosylarylimines by using chiral diphosphane ligands. A number of commercial diphosphane ligands were screened. Despite moderate to good yields, *ee* values of 99% could be achieved with MeDuPhos. Novel Rh^{I} catalysts were also screened, and *ee* values as high as 74% could be obtained.

Introduction

The formation of carbon–carbon single bonds is one of the most fundamental, yet important reactions in organic synthesis. The addition of specific carbon nucleophiles to appropriate functionalities, like C=O, C=C and C=X is an attractive synthetic methodology for forming C–C bonds. In fact, the addition of arylboronic acids to arylimines in the presence of appropriate catalysts, like (phosphane)rhodium(I) complexes is a very attractive method for forming C–C bonds under very mild conditions, and at the same time, introducing the amino functional group in the product.[1] Due to the large variety of arylboronic acids, which are commercially available, a large array of α-arylamines can be quickly assessed by using this method. Many α-arylamines are known to be biologically active and are thus present in a number of natural products and drugs. For instance, (*S*)-ceterizine (Figure 1), an antihistaminic approved drug to treat allergic symptoms, can be obtained by using a diarylmethylamine precursor as a potential key intermediate.[2]

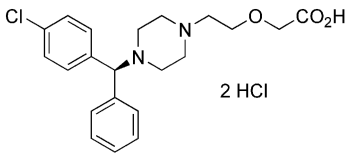

Figure 1. (*S*)-Ceterizine (Zyrtec®).

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901139.

Despite the attractiveness of this approach, catalytic asymmetric imine arylations with boronic acids still have yet to be fully exploited. In 2004, Tomioka and co-workers reported the arylation of *N*-tosylimines with both arylboronic acids and arylboroxines using Rh^{I} catalysts formed from a variety of novel *N*-Boc-L-valine amidomonophosphanes and (*S*)-BINAP.[3] The best result obtained was 92% *ee*. (*S*)-BINAP could only afford a maximum *ee* of 34%. In the same year, Hayashi's group reported the arylation of *N*-tosylimines with arylboroxines using chiral rhodium(I) catalysts that contain C_2-symmetric bicyclo[2.2.2]octadienes;[4] *ee* values as high as 99% were obtained. It was demonstrated that the *ee* values obtained with commercial chiral diphosphane ligands, like (*R*)-BINAP (31% *ee*), (*R*)-segphos (70% *ee*) and (*S*)-phosphoramidite (6% *ee*), were lower. The main disadvantages of this method are that the chiral diene must first be synthesised in order to prepare the chiral ligand, and toxic arylboroxines are used as reagents. Zhou and co-workers[5a] demonstrated the highly enantioselective addition of arylboronic acids to *N*-tosylarylimines catalysed by Rh complexes containing a spiro monophosphite ligand (*S*)-ShiP in aqueous media. The addition product was obtained in good yield (77%) and with high *ee* (93%). Gennari's group[5b] has reported the use of chiral binaphtholic phosphate and phosphoramidite ligands for the Rh^{I}-catalysed arylation of some *N*-tosylimines. The best *ee* values (76–99%) were obtained with the former ligands.

Afterwards, Xu and co-workers[6a] developed and tested a new type of C_2-symmetric chiral diene ligands, which proved to be a remarkably efficient ligand for asymmetric arylation of *N*-tosylarylimines using arylboronic acids. They obtained excellent enantioselectivities (98%). Trincado and Ellman[7] later made some changes to the procedure and tested several known chiral phosphanes, of which (*R*,*R*)-deguphos (**5**) (Figure 2) gave the best results. They concluded that pre-incubating the ligand, the precata-

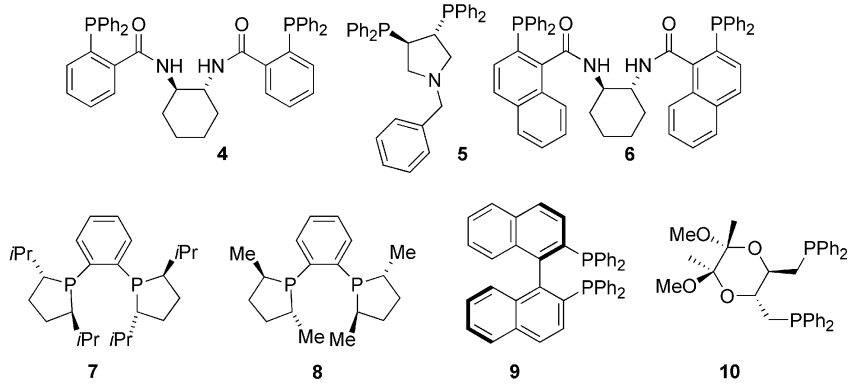


Figure 2. Chiral phosphane ligands screened.

lyst and the arylboronic acid for 90 min prior to the addition of the substrate improved the yield, but, in some cases decreased the enantioselectivity.

The application of palladium catalysts for catalytic asymmetric imine arylation is very poorly developed, and there are only a few reports in the literature as far as we are aware. Shi and co-workers[8a] reported on the application of C_2-symmetric cationic diaquo(NHC)Pd^{2+} complexes, where *ee* values of up to 94% have been achieved. Dai and Lu[8c] reported the first application of the diphosphane ligands SEGPHOS and BINAP in an attempt to phenylate *N*-tosyl-*p*-nitrophenylimine. However, the reaction failed. Besides offering such versatility for carbon–carbon bond formation,[9] Pd is a cheaper metal than rhodium and less toxic.

In this paper we wish to report our work with various chiral Pd and Rh catalysts for the catalytic asymmetric arylation of selected *N*-tosylimines.

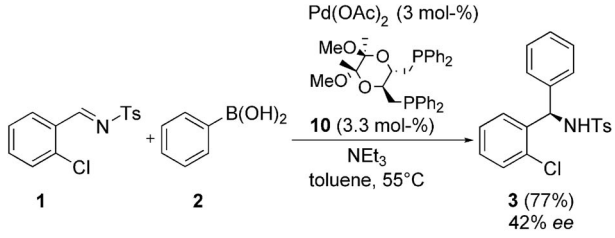
Results and Discussion

Initially, we looked at the effect and potential of palladium for this useful transformation. Lu and Dai have shown that *N*-tosylarylimines with strong electron-withdrawing groups are the best substrates for this reaction.[5c] For this reason we chose *N*-tosyl-*o*-chlorophenylimine as our substrate. $Pd(OAc)_2$ was used as the palladium source.

We investigated the reaction of the *N*-tosyl-*o*-chloroarylimine **1** with phenylboronic acid (**2**) in the presence of $Pd(OAc)_2$ (3 mol-%), Berens' DIOP analogue **10** and a base in toluene at 55 °C (Scheme 1). Berens' DIOP analogue **10** has been studied in a number of catalytic asymmetric reactions, like hydrogenation,[10a] asymmetric allylic alkylation,[10b] hydroboration[10c] and hydrosilylation.[10c] Gratifyingly as a first attempt, we could obtain the addition product **3** in 77% yield and with an *ee* of 42% (Scheme 1). The enantioselection favoured the (*R*) enantiomer.

We conducted a solvent screening study to determine if there were any solvent effects. The results are shown in Table 1.

This study showed that the reaction could be conducted in almost all the solvents described in Table 1, with the exception of CH_3CN and DMF. The yield decreased for all



Scheme 1. Asymmetric phenylation of *N*-tosylarylimine **1** with phenylboronic acid (**2**).

Table 1. Solvent screening reactions.

Entry	Solvent	Time [h]	η[a] [%]	*ee*[b] [%]
1	dioxane	20	24	10 (*R*)
2	$CHCl_3$	20	26	17 (*R*)
3	MeOH	20	13	45 (*R*)
4	DMF	20	<10	<5 (*R*)
5	THF	22	30	38 (*R*)
6	CH_2Cl_2	22	26	46 (*S*)
7	CH_3CN	22	<5	81 (*R*)

[a] Isolated yields. [b] Determined by HPLC using an AD column, *n*-hexane/2-propanol (90:10) at 0.7 mL/min, with wavelength detector at 230 nm.

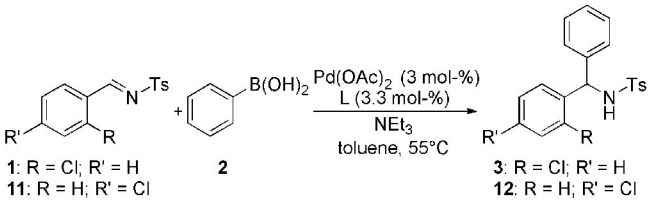
the solvents, despite the *ee* increasing slightly for some solvents, like MeOH, CH_2Cl_2 and CH_3CN (Table 1, Entries 3, 6 and 7, respectively). We believe that hydrolysis of the tosylimine was the main side reaction,[5c] which becomes kinetically more favourable in polar, coordinating solvents like MeOH, DMF and CH_3CN. Toluene is therefore the solvent of choice. The switch in the configuration of the major enantiomer to (*S*) on using CH_2Cl_2 (Table 1, Entry 6) was surprising and implied a structural change in the active catalyst and/or the mechanism in this case.

A diverse range of diphosphane ligands were then screened (Figure 2). These included Trost's ligands **4** and **6**, which have been very successful in the palladium-catalyzed asymmetric allylic alkylation reaction,[11] (*R*,*R*)-Me-DuPhos (**8**), which has also been very successful in the same reaction[12,13] and Berens' ligand **10**, which also has been quite good for Pd-catalysed reactions.[10b]

We screened the ligands with both *N*-tosyl-*o*-chloroarylimine **1** and *N*-tosyl-*p*-chloroarylimine **11** under the same conditions as described in Scheme 1.

By analysing the results obtained it could be seen that, generally speaking, the yields were moderate to good, with a highest of 77% (isolated) achieved (Table 2, Entry 12). The highest yields were achieved with **1**, which indicated that electronic effects were quite important. In fact, on using *para* substrate **11**, the yields were very poor, see for example Entry 3 (Table 2).

Table 2. Asymmetric phenylations of *N*-tosylimines **1** and **11** with phenylboronic acid and ligands **4**–**10**.

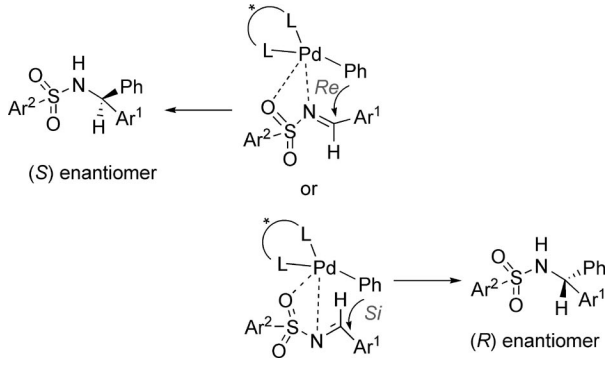


Entry	Substrate	Ligand	Time [h]	η[a] [%]	*ee*[b,c] [%]
1	**1**	**4**	70	27	82 (*R*)
2	**1**	**5**	41	57	72 (*R*)
3	**11**	**5**	40	<10	12 (*R*)
4	**1**	**6**	70	22	69 (*S*)
5	**11**	**6**	40	16	29 (*S*)
6	**1**	**7**	70	21	92 (*S*)
7	**11**	**7**	40	n.r.[d]	n.r.
8	**1**	**8**	70	41	>99 (*S*)
9	**11**	**8**	40	19	11 (*S*)
10	**1**	**9**	45	29	<5 (*S*)
11	**11**	**9**	45	10	<10 (*S*)
12	**1**	**10**	23	77	42 (*R*)
13	**11**	**10**	45	22	41 (*R*)

[a] Isolated yields. [b] Determined by HPLC by using an AD column, *n*-hexane/2-propanol (90:10) at 0.7 mL/min for substrate **1** and OD-H column, *n*-hexane/2propanol (93:7) at 0.7 mL/min for substrate **11**, both with wavelength detector at 230 nm. [c] The absolute configurations were determined by comparing the data with those already know in the literature. [d] No reaction.

Regarding the enantioselectivity of these reactions. Some very good to excellent *ee* values could be obtained. Overall it was substrate **1**, which gave the best *ee* values, and we attribute this to both electronic and sterochemical effects; for example, >99% *ee* with Me-DuPhos (**8**) (Table 2, Entry 8) using **1** as substrate and 92% *ee* using *i*Pr-DuPhos (**7**) as ligand with the same substrate (Table 2, Entry 6). The fact that less bulkier **8** gave higher *ee* values than **7** might imply the intervention of a more compact Pd catalyst in the former case. Surprisingly, although the phosphanes **7** and **8** have the opposite absolute configurations, the major amine enantiomer had the (*S*) configuration in each case. In fact, it was (*S*)-BINAP, which gave the lowest *ee* values, accompanied by low yields. However, this would be expected on the basis of Dai and Lu's[5c] results with *N*-tosyl-*p*-nitrophenylimine, and is in agreement with that of Zhou and coworkers, who achieved an *ee* of 10% with **11** as substrate, even though the pre-catalyst used was Rh(acac)$(CH_2$-$CH_2)_2$.[5a] Berens' ligand **10** gave moderate *ee* values of 42 and 41%, respectively (Table 2, Entries 12 and 13). Trost's ligands **4** and **6**, which are excellent for palladium-catalyzed allylic alkylations,[11] gave *ee* values of 82% and 69%, respectively (Table 2, Entries 1 and 4) with substrate **1**.

We have proposed the following working model to explain the resulting product configuration. This model was based partly on information furnished in Shi's paper.[8a] Due to the overall configuration of the key Pd^{I}–aryl species containing Trost's naphthyl ligand **6** or the DuPhos ligands **7/8** or the BINAP ligand **9** (which are expected to coordinate with the arylimine in the mode suggested in Scheme 2) the phenyl group will be delivered from the catalyst to the imine via *Re*-face attack with preferential formation of the (*S*)-amine enantiomer. Then delivery of the aryl group to the imine will occur by *Si*-face attack resulting in the preferential formation of the (*S*)-amine enantiomer (Scheme 2). In the case of Trost's phenyl ligand **4**, or the DeguPhos ligand **5**, or Berens' ligand **10** the aryl group is expected to be delivered by *Si*-face attack resulting in the preferential formation of the (*R*)-amine enantiomer (Scheme 2).



Scheme 2. Working model to explain the differential stereochemical outcomes by using different diphosphane ligands.

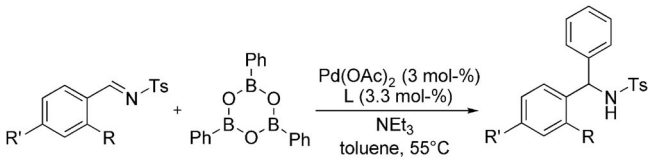
In an attempt to block imine hydrolysis,[15] the phenylboroxine **13** was investigated as the phenyl source. The results are highlighted in Table 3. Both **1** and **11** were used as substrates and **7** and **10** as ligands.

Concerning Berens' ligand **10**, the best result was achieved by using boroxine **13** and molecular sieves (Table 3, Entry 5). Compared with Entry 12 (Table 2) this method makes a significant difference, with both the yield and the *ee* remarkably improved. Like in the case of using phenylboronic acid (**2**) (Table 2, Entries 12 and 13) the aryl group is expected to be delivered by *Si*-face attack resulting in preferential formation of the (*R*)-amine (Scheme 2).

It was found that the yields increased on using phenylboroxine and molecular sieves as compared to using only phenylboroxine. With the bulkier *i*Pr-DuPhos ligand (**7**) the yield increased for all the reactions, although the enantioselectivities remained quite low.

Using the method of Zhou[5a] we have also screened some rhodium(I) catalysts with Berens' ligand **10**. Although the yields were quantitative, we could only achieve an *ee* as high as 16% using $[RhCl(COD)]_2$ with the *N*-tosyl-*o*-

Table 3. Asymmetric phenylations of *N*-tosylimines **1** and **11** with boroxine **13** and ligands **7** and **10**.



1: R = Cl; R' = H
11: R = H; R' = Cl

13

3: R = Cl; R' = H
12: R= H; R'= Cl

Entry	Substrate	Ligand	Mol. sieves (3 Å) [mg]	Time [h]	η[a] [%]	*ee*[b,c] [%]
1	**1**	**10**	none	44	< 10	36 (*R*)
2	**11**	**10**	none	44	27	40 (*R*)
3	**1**	**7**	none	44	27	38 (*S*)
4	**11**	**7**	none	44	< 10	<5 (*R*)
5	**1**	**10**	200	64	99	64 (*R*)
6	**11**	**10**	200	64	64	37 (*R*)
7	**1**	**7**	200	64	38	<5 (*S*)
8	**11**	**7**	200	64	29	<10 (*R*)

[a] Isolated yields. [b] Determined by HPLC using an AD column, *n*-hexane/2-propanol (90:10) at 0.7 mL/min for substrate **1** and OD-H column, *n*-hexane/2-propanol (93:7) at 0.7 mL/min for substrate **11**, both with wavelength detector at 230 nm. [c] The absolute configurations were determined by comparing the data with those already know in the literature.

chloroarylimine **1** and KF as base in toluene/water. However, when the reaction was conducted in the absence of water (with toluene as solvent) and triethylamine as base the *ee* dropped to 9% and the yield to 33%. This indicated that the presence of water was important somewhere in the catalytic cycle. On turning to $[Rh(COD)_2BF_4]_2$ with triethylamine as base in toluene, we could increase the *ee* up to 74%, despite obtaining a yield of only 14%. Analysis of the Rh pre-catalyst showed that it contained approx. 5.5% water, which was amassed during storage. When a fresh anhydrous sample of $[Rh(COD)_2BF_4]_2$ was used the *ee* was only 6%, but the yield had increased to 34%. This result is hard to explain, but implies that in the case of $[Rh(COD)_2BF_4]_2$ substoichiometric quantities of water promote higher enantioselection and at the same time, retard reaction efficiency. The actual mechanism is currently under investigation.

Conclusions

We have provided the first account of the successful application of a range of chiral diphosphane ligands in the palladium-catalysed arylation of electron-deficient *N*-tosylimines using both phenylboronic acid and phenylboroxine. An *ee* of >99% could be obtained with Me-DuPhos. The use of phenylboroxine in concert with molecular sieves increased the reaction yield.

Preliminary screening studies of some Rh^I catalysts were quite encouraging. They indicated the importance of water for catalyst activation.

Further studies are underway at screening other ligand types, like novel chiral NHCs, in this reaction.

Experimental Section

General Remarks: All reactions were performed under an inert gas, all the reagents were obtained from Aldrich, Fluka and Acros, and all the solvents were dried by using standard laboratory methods. The substrates **1** and **11** and phenylboroxine **13** were prepared by using literature procedures.[14,16] Berens' ligand **10** was provided by ChiraTecnics, Lda. Racemic products for chiral HPLC analysis were prepared from the corresponding *N*-tosylimines (0.5 mmol) with phenylboronic acid (1.0 mmol) in the presence of $Pd(OAc)_2$ (5 mol-%) and 2,2′-bypiridine (10 mol-%) in dioxane (1.5 mL) at 100 °C for 48–72 h.

General Procedure for the Catalytic Asymmetric Arylation of *N*-Tosylarylimines with Phenylboronic Acid or Phenylboroxine: Toluene (1.0 mL) was added to a round-bottom flask charged with phenylboronic acid or phenylboroxine (0.4 mmol), pre-catalyst (3 mol-%) and chiral ligand (3.3 mol-%) under nitrogen. The mixture was heated to 55 °C and stirred for 30 min. *N*-Tosylarylimine (0.2 mmol), toluene (1 mL) and NEt_3 (0.4 mmol) were added sequentially. After the mixture was stirred for 55 °C during 24–48 h, HCl (0.2 M, 5 mL) was added to quench the reaction. The mixture was extracted with EtOAc and washed with brine. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel column chromatography to afford the desired diarylamine product.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data.

Acknowledgments

We are grateful for financial support from the Fundação para a Ciência e a Tecnologia (FCT) (project PPCDT/QUI/55779/2004) through POCI 2010, supported by the European Community fund FEDER. The FCT is also acknowledged for the award of a PhD grant to C. S. M. (SFRH/BD/45132/2008). The personnel of the NMR units of INETI (Lisbon, Portugal) and CACTI (Vigo, Spain) are gratefully acknowledgment for NMR analysis.

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Received: October 8, 2009
Published Online: February 11, 2010

