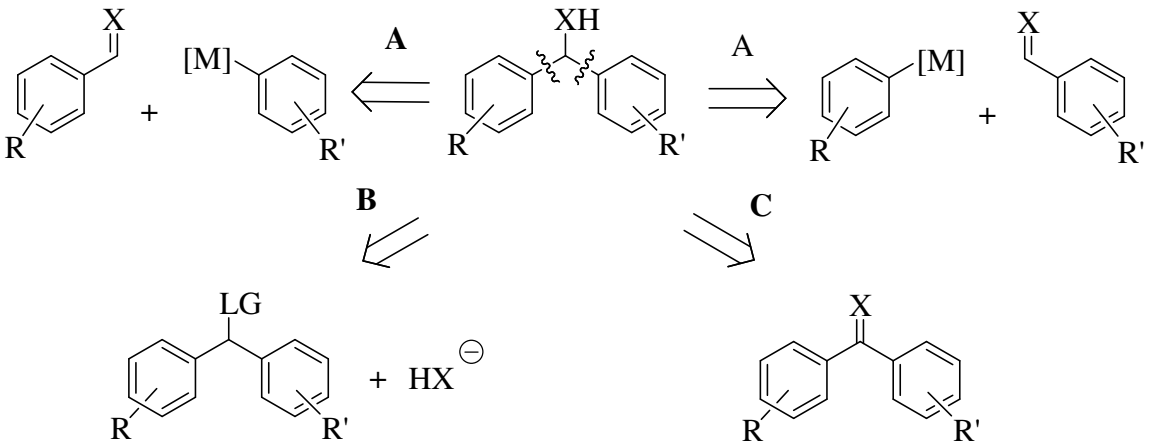
Chapter 5
Asymmetric Aryl Transfer to Imines: Synthesis of Diarylmethylamines

5.1. Introduction

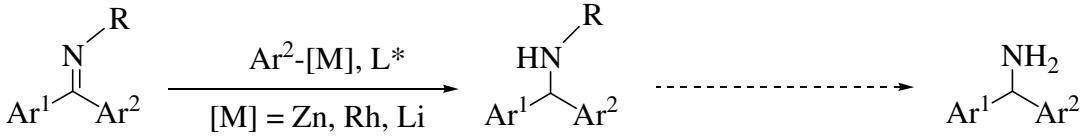
As specified in Chapter 4, control of the stereochemistry in the formation of chiral diarylmethanols has attracted considerable interest over the past 20 years.

Enantiopure diarylmethylamines are also important intermediates for the synthesis of biologically active compounds. As a consequence, many efforts have been made for the synthesis of these molecules.

Several routes allow access to these compounds (scheme below): i) carbon-carbon bond formation of aromatic arylimines and the appropriate organometallic compounds (path **A**); ii) nucleophilic displacement at the benzylic position (path **B**); iii) or reduction of C=N bond of the corresponding diarylketimines (path **C**).

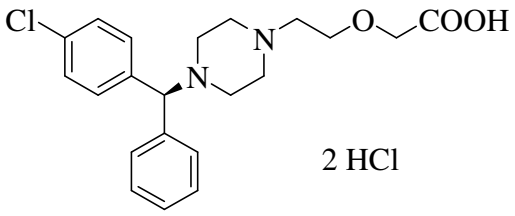


In the case of diarylmethylamines efficient catalytic asymmetric reductions of the corresponding diarylimines are still lacking and only the enantioselective aryl transfer reaction to aldimines has been developed. This usually involves chiral rhodium complexes, or, alternatively, is catalysed by chirally modified lithium or zinc reagents:



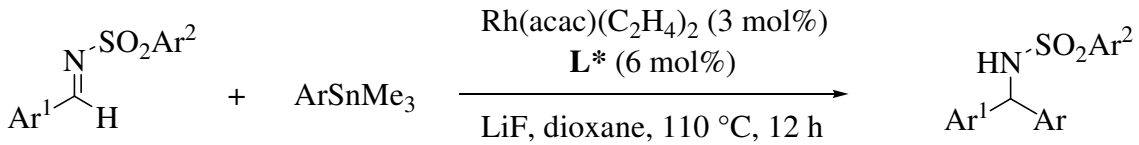
Addition to aldimines

An example of a diarylmethylamine which is precursor for a compound with physiologically interesting properties is the second-generation histamine H_1 antagonist cetirizine hydrochloride (Zyrtec®). Significantly, only the (*S*)-enantiomer of the this compound is biologically active (**5.1**), and it has therefore been marketed in enantiopure form since the beginning of 2002 (Levocetirizine Xyzall®).

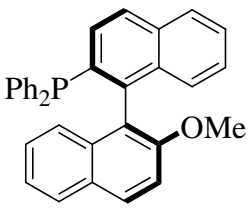


5.1

The first catalysed asymmetric aryl transfer reaction onto imines, resulting in the formation of optically active diarylmethylamines with high enantiomeric excesses, was reported by Hayashi in 2000.[1] *N*-Arylsulfonylimines served as substrates in a rhodium(I)-catalysed process with arylstannanes as aryl source. Monodentate phosphines (*R*)-MeO-MOP **5.2** or (*R*)-Ar*-MOP **5.3** were the most effective ligands.

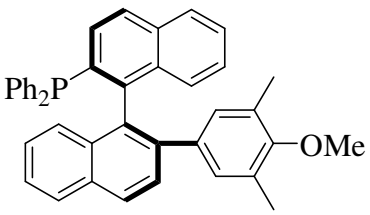


(*R*)-MeO-MOP



5.2

(*R*)-Ar*-MOP

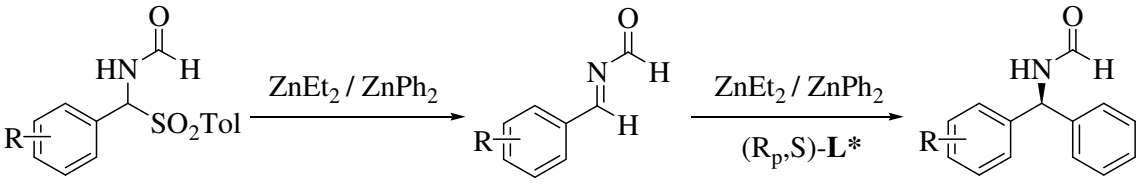


5.3

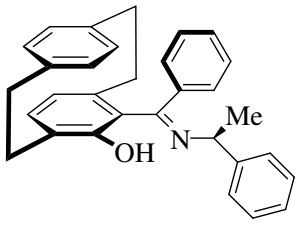
The substituent in the *para*-position of the sulfonyl arene (Ar^2) determined the reactivity of the aryl-accepting imines. The presence of more electron-withdrawing substituent (for example a NO_2 group) led to higher enantiomeric excesses and better yields of the resulting diarylmethylsulfonamides. Also the aromatic substituent (Ar^1) of the imine played an important role: the aryl transfer onto electron poor imines (Ar^1 = *p*-F_3CPh, *p*-

MeO_2CPh, *p*-ClPh and *p*-FPh) furnished the products with excellent enantioselectivities (≥ 96%) in very high yields (≥ 90%). In contrast the unsubstituted imine, derived from benzaldehyde (with Ar^1 = Ph), gave the products with (only) up to 92% *ee* in 86% yield. Also, the type of phosphine ligand was crucial in this reaction. When chelating bisphosphine such as BINAP and DIOP were used, the reaction was very slow and the product could at best be isolated in only 10% yield with up to 6% *ee* Compared to catalyses with rhodium complexes bearing MeO-MOP as ligand, improved enantioselectivities and higher yields were achieved in reactions with the slightly modified phosphine like Ar*-MOP. Synthetically important is the fact that products with N-nosyl groups (SO_2Ar^2 = Ns) easily afforded primary amines in good yields upon removal of the protecting group by reaction with benzenethiol and K_2CO_3 in DMF.

An alternative approach to asymmetric phenyl transfer reactions onto imines was described by Bolm and Bräse in 2002.[2] There, *in situ* formed N-formylimines accepted aryl groups from mixtures of diphenyl- and diethylzinc. After screening several catalysts based on ferrocene, cyrhetrene and other N,O-chelates having [2.2]paracyclophane backbones, **5.4** was identified as the most effective catalyst for this reaction. The substrates, N-formylimines, were formed *in situ* by deprotonation of amides and subsequent elimination of the sulfinate.



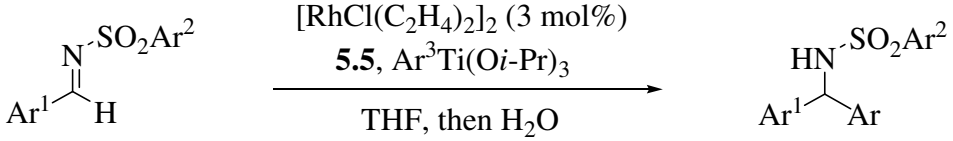
5.4



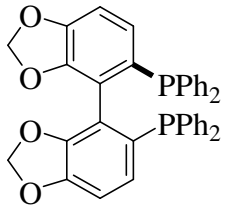
The best result was obtained with *p*-tolylamide amide (with R = 4-Me) in combination with 10 mol% of **5.4** in toluene at -20 °C, which led to the product with 97% *ee* in 98% yield. Various electronic and steric modifications of the aryl acceptors were tolerated.

Compounds with electron rich, electron poor and bulky substituents on the aromatic ring gave excellent results with enantioselectivities up to 95% *ee*. However, *meta*-substituted substrates resulted in slightly lower enantiomeric excesses.

In 2004, Hayashi demonstrated rhodium-catalysed diaryl-methylamine formations with titanium reagents as aryl sources.[3] There, complexes with Segphos **5.5** as ligand were applied, and *N*-Arylsulfonylimines with Ar^1 = Ph and aryltitaniumtriisopropoxides with Ar^3 = 4-Ph served as starting materials.



Ar^1 = Ph, Ar^3 = 4-Ph

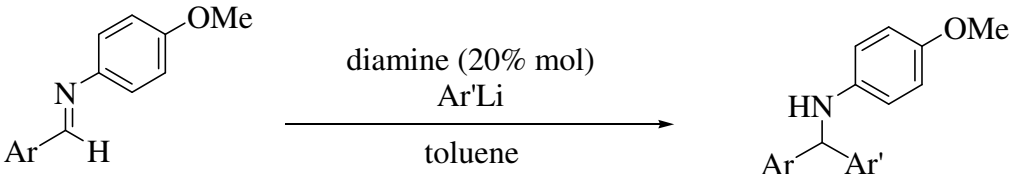


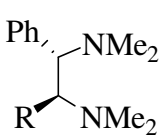
5.5

The latter are highly reactive towards transmetalation and form aryl rhodium species, which are capable of transferring the aryl group to the imine in an enantioselective fashion. Sterically demanding sulfonylaryl groups having three isopropyl substituents on the aromatic ring were essential for achieving high enantioselectivities. A wide range of neutral, electron rich and electron poor imines as well as a variety of titanium reagents proved applicable.

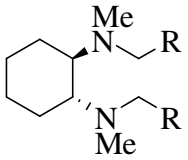
Recently, asymmetric addition of aryllithium reagents to aromatic imines in the presence of C_2-symmetric diamines such as **5.6** and **5.7** have been described.[4] Although in some cases an excess of the ligands was required, their amount could often be reduced to substoichiometric quantities (20 % mol) without significant loss of enantioselectivity. Several diamines were tested and products with up to 84% *ee* (at

19% conversion) were obtained using 20% mol of *N*,*N*,*N*',*N*'-tetramethylcyclohexyl-1,2-diamine (with R = H) in toluene at -78 °C.



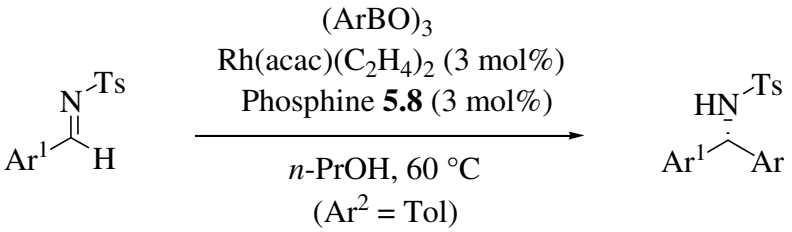


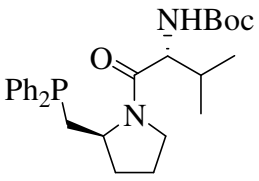
5.6



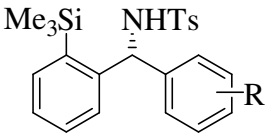
5.7

In 2004, Tomioka reported the catalytic asymmetric aryl transfer reaction onto N-tosylarylimines (with SO_2Ar^2 = Ts) with arylboroxines as aryl sources.[5] The reaction was catalysed by a rhodium(I) complex bearing the L-valine-derived amidomonophosphane as chiral ligand **5.8**.





5.8

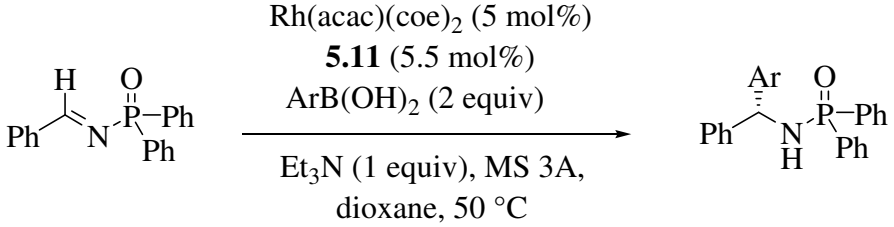


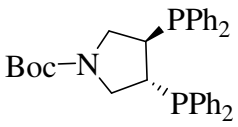
5.9: R = 3-Cl
5.10: R = 4-OMe

The enantiomeric excesses of the resulting tosylamines were found to be dependent on the substitution pattern of Ar^1. The best result (94% *ee*, 99% yield) was achieved in the formation of amine **5.9**. In this catalysis, trimethylsilyl-substituted arylimine served as starting material, which reacted with *m*-chlorophenylboroxine in *n*-propanol at 60 °C.

Also, an electron rich boroxine [(*p*-MeOPhBO)$_3$] was successfully applied in this addition reaction forming **5.10** in 90% *ee* and 87% yield.

Recently, a rhodium-catalysed, asymmetric addition reaction of arylboronic acids to *N*-diphenylphosphinoyl aldimines was described by Ellman.[6] This study also included a diastereoselective variant of this reaction using a chiral auxiliary. After screening several diphosphines, (*R*,*R*)-DeguPHOS **5.11** was found to be the most effective ligand, giving phosphinic amides with up to 96% *ee* in high yield.

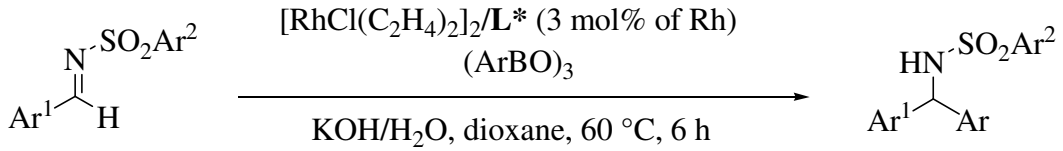


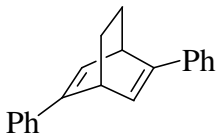


5.11 = (*R*,*R*)-DeguPHOS

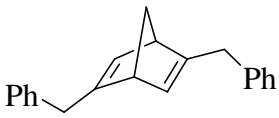
Interestingly, acceptable conversions of the imine were only observed with diphosphine ligands having a two-atom spacer between the two diphenylphosphino substituents or a binaphthyl backbone. Other ligands such as Josiphos, Walphos and DIOP gave very low conversions.

Another example is the phosphine-free rhodium catalysis reported by Hayashi in 2004.[7] With C_2-symmetric bicyclo-[2.2.2]octadienes (bod*) or bicycle [2.2.1]heptadiene (Bn-nbd*) **5.13** as ligands, the asymmetric aryl transfer reaction between N-tosylarylimines and aryl boroxines proceeded smoothly within 6 h at 60 °C. The catalyst was generated from [RhCl(C_2H_4)$_2$]$_2$ (3 mol % of Rh), aqueous KOH (20 mol %) and the chiral diene (3 mol %) in dioxane. Using *p*-chlorophenylboroxine (with Ar = 4-ClPh) as the aryl source and N-tosylphenylimine as aryl acceptor, the rhodium catalyst generated from Ph-bod* **5.12** led to the corresponding amine with excellent *ee* (99%) in very high yield (99%).



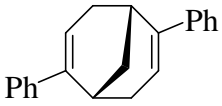


L* = Ph-bod*
5.12



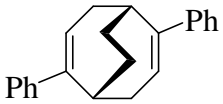
L* = Bn-nbd*
5.13

In subsequent studies, Hayashi described the use of 2,6-diphenylbicyclo[3.3.1]nona-2,6-diene (Ph-bnd*) **5.14** and 2,6-diphenylbicyclo[3.3.2]deca-2,6-diene (Ph-bdd*) **5.15** in this rhodium-catalysed aryl transfer reaction.



L* = Ph-bnd*

5.14



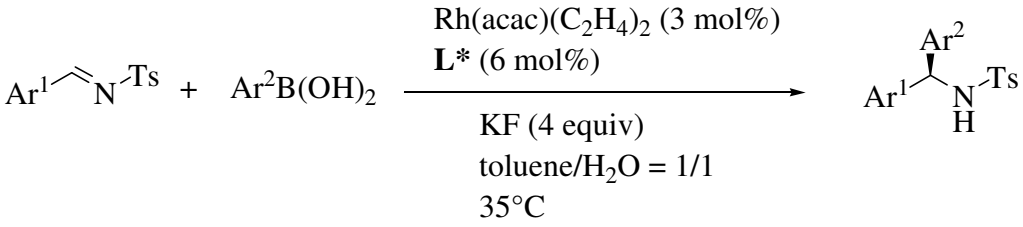
L* = Ph-bdd*

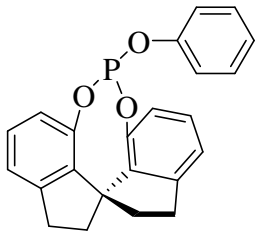
5.15

N-Nosyl-protected arylimines (with $Ar^2 = C_6H_4(NO_2)$) could also be applied, giving the corresponding products with up to 99% *ee* in almost quantitative yield. The catalyst with Ph-bnd* **5.14** as ligand showed the highest enantioselectivity for both nosyl and tosyl protected imines. In general, all rhodium complexes with diene ligands showed higher activities than those bearing phosphine as ligands.

More recently, monodentate phosphite ligands have been used by Zhou and coworkers in the highly enantioselective (*ee*'s 85-96%) addition of arylboronic acids to *N*-tosylarylimines,[8] while the group of de Vries, Feringa and Minnaard reported good enantioselectivities (*ee*'s 82-94%) in the rhodium-catalyzed arylation of *N,N*-dimethylsulfamoylarylimines, using monodentate phosphoramidite ligands.

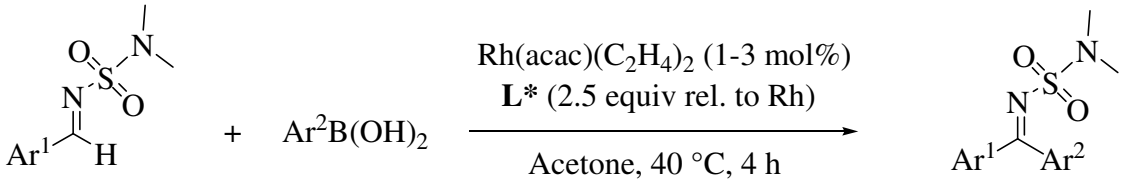
The group of Zhou obtained the best result with *N*-tosyl-1-naphthaldehyde imine (Ar^1 = 1-naphthyl) and using the spiro-phosphite **5.16** reported in the scheme below:





5.16

The group of Minaard and Feringa got the best enantioselectivities with *para*-chlorobenzaldimine (Ar^1 = 4-ClC_6H_4) and using the phosphoramidite **5.17**.



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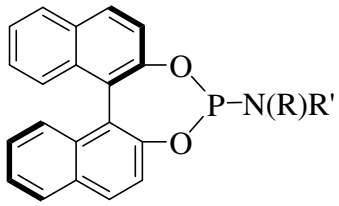
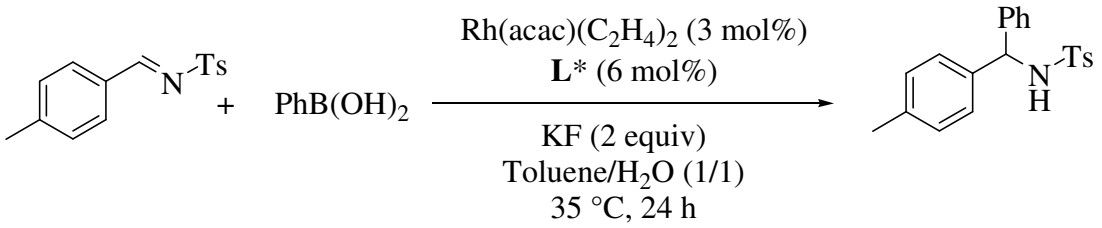


R = H, R' = 4-$MeOC_6H_4$

L* = 5.17

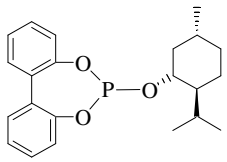
5.2. Enantioselective rhodium-catalysed addition of arylboronic acids to *N*-tosylarylimines

A library of chiral biphenolic and binaphtholic phosphites and phosphoramidites 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:



As discussed in Chapter 4, Zhou reported his results about the arylation of *N*-tosylarylimines using the same conditions and ligands tested on aldehydes obtaining a more efficient catalytic system and higher values of *ee* (up to 96%).

The ligands tested by our group and the results obtained are reported in the tables below (the ligands were tested either individually or as binary combinations (L_a/L_b 1:1, 3 mol% each):



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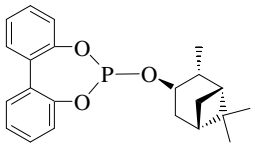

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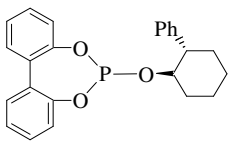

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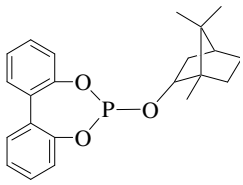

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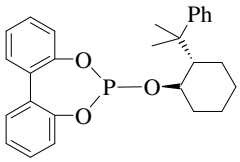

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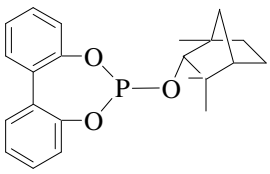

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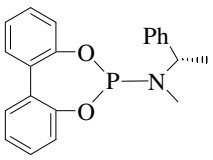

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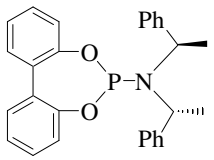

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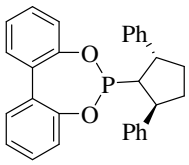
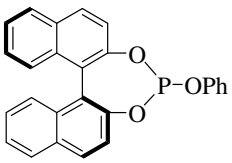
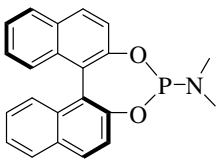
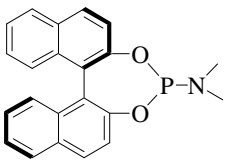
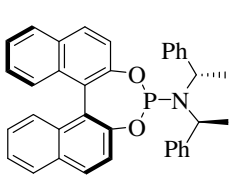
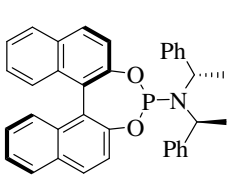
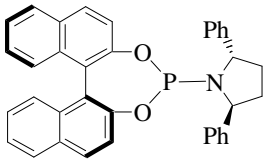








3.43 **3.44** **3.46** **3.47**

3.48 **3.49** **3.50**

Entry	L_a	Yield (%)	*ee* (%)
1	**3.26**	-	-
2	**3.27**	42	3 (*R*)
3	**3.28**	-	-
4	**3.29**	79	8 (*S*)
5	**3.30**	-	-
6	**3.33**	19	7 (*S*)
7	**3.38**	50	23 (*S*)
8	**3.36**	33	22 (*R*)
9	**3.43**	61	80 (*S*)
10	**3.44**	87	40 (*S*)
11	**3.46**	90	27 (*S*)
12	**3.48**	60	94 (*S*)
13	**3.49**	-	-
14	**3.50**	25	96 (*S*)
15	**3.47**	87	26 (*R*)

In general, biphenolic phosphites are not selective and sometimes are completely not active as ligands (entries 1-6). Biphenolic phosphoramidites were more selective than phosphites and ligand **3.43** afforded the product with 80 % *ee* (entries 7-9).

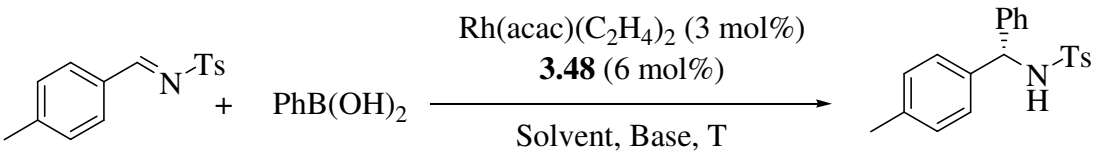
Good enantiomeric excesses were obtained with binaphtholic phosphoramidite ligands containing a bulky chiral amine (i.e. ligands **3.48** and **3.50**; entries 12 and 14). Unfortunately, the yields were only moderate for most of the ligands, especially for those which showed the higher selectivity (good yields were obtained with the binaphtholic phosphite **3.44** and Monophos® entries 10, 11 and 15).

In addition, several ligand combinations were screened to investigate the presence of possible cooperative effects.

Entry	L_a	L_b	Yield (%)	*ee* (%)
1	**3.44**	**3.48**	17	49 (*S*)
2	**3.44**	**3.46**	95	50 (*S*)
3	**3.44**	**3.49**	-	-
4	**3.48**	**3.27**	50	61 (*S*)
5	**3.44**	**3.38**	56	2 (*R*)
6	**3.46**	**3.43**	55	24 (*S*)

When binaphtholic phosphite **3.44** [yield = 87%, *ee* = 40% (*S*)] and Monophos® **3.46** [yield = 90%, *ee* = 27% (*S*)] were used in combination, a small cooperative effect was observed [yield = 95%, *ee* = 50% (*S*); entry 2]. Although the increase of *ee* obtained by the combination 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.

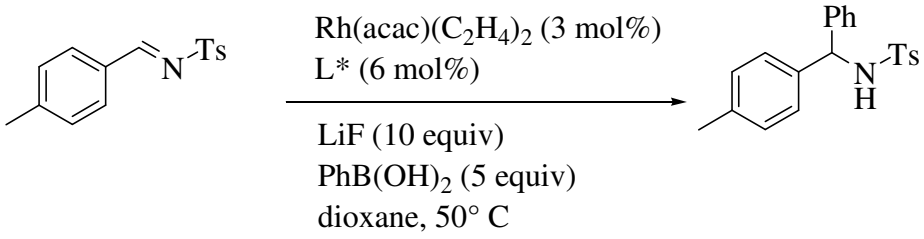
Encouraged by the *ee*'s obtained with ligands **3.48** and **3.50**, we decided to screen different reaction conditions (solvent, base and temperature) using ligand **3.48** (more easy to be synthesized), in order to improve the yields of the reaction.



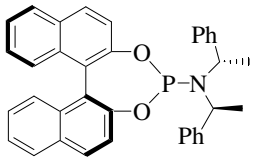
Entry	Solvent	Base (eq)	$PhB(OH)_2$	Temp (°C)	Yield (%)	*ee* (%)
1	toluene	LiF (10)	5 equiv.	110	n.p.	/
2	THF:H_2O 1:1	KF	3 equiv.	50	n.p.	/
3	diox:H_2O 10:1	LiF (10)	3 equiv.	50	n.p.	/
4	diox:H_2O 1:2	Et_3N	2 equiv.	RT	n.p.	/
5	acetone	/	1.3 equiv.	40	n.p.	/
6	dioxane	/	5 equiv.	reflux	40	40
7	dioxane	KOH	3 equiv.	50	n.p.	/
9	dioxane	LiF (10)	3 equiv.	50	55	87
10	dioxane	LiF (10)	5 equiv.	RT	n.p.	/
11	dioxane	LiF (10)	5 equiv.	reflux	95	76
12	**dioxane**	**LiF (10)**	**5 equiv.**	**50**	**78**	**87**

While no improvement was observed using numerous solvent-base combinations [dry 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's were finally obtained using anhydrous dioxane with LiF as base (entry 12).[9]

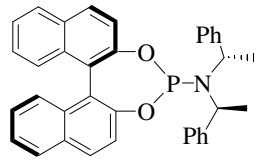
The new reaction conditions are summarized in the scheme below:



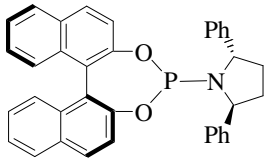
A small sub-library of phosphoramidite ligands (figure below) was then tested under these optimized conditions in the addition of phenylboronic acid to *N*-tosyl-*p*-tolylaldehyde imine. Since the presence of a bulky amine derivative was apparently necessary to obtain a high *ee*, we decided to include **3.50**, the two ligands **3.49** (distereomer of **3.48**) and **3.51** (the diastereomer of **3.50**), the biphenolic ligand **3.43** to test the effective role of the amine moiety in this reaction and, finally, the binaphtholic phosphoramidite **3.52** derived from bis(1-naphthylethyl)amine (see the table below)



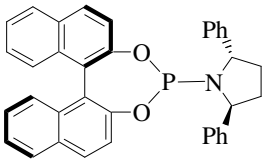
3.48



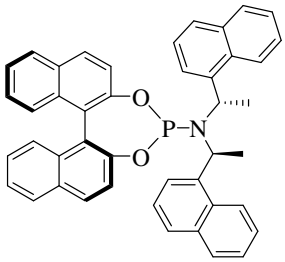
3.49



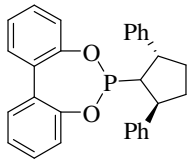
3.50



3.51



3.52



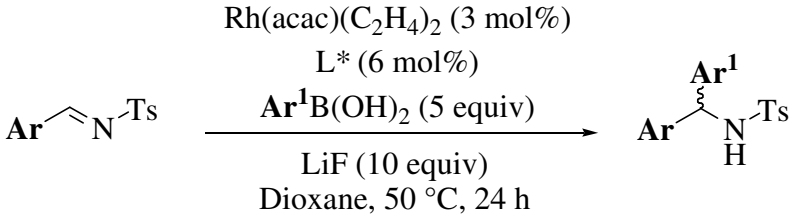
3.43

Entry	L*	Yield (%)	*ee* (%)
1	**3.48**	60	87 (*S*)
2	**3.49**	21	33 (*R*)
3	**3.50**	93	90 (*S*)
4	**3.48**	82	86 (*S*)
5	**3.43**	65	84 (*S*)
6	**3.52**	15	76 (*R*)

A clear matched combination of the binaphthol chiral axis and of the amine stereocenters is observed for phosphoramidite **3.48** (S_a,*S*,*S*) [yield = 60%, *ee* = 87% (*S*); entry 1] with respect to **3.49** (R_a,*S*,*S*) [yield = 21%, *ee* = 33% (*R*); entry 2]. On the contrary, in the case of **3.50** (S_a,*S*,*S*) and **3.51** (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 **3.43**, which is devoid of the chiral axis. Ligands **3.50** and **3.43** have already been used by us[10,11] and others[12] as very effective ligands in different reaction processes. Ligand **3.52** (S_a,*S*,*S*),[13] 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 **3.48** and **3.50**:



Entry	Ar	Ar^1	L*	Conv. (%)	*ee* (%)
1	2-Me-C_6H_4	Ph	**3.48**	54	78 (*S*)
2	2-Me-C_6H_4	Ph	**3.50**	42	71 (*S*)
3	4-OMe-C_6H_4	Ph	**3.48**	40	89 (*S*)
4	4-OMe-C_6H_4	Ph	**3.50**	70	81 (*S*)
5	3-OMe-C_6H_4	Ph	**3.48**	57	82 (*S*)
6	3-OMe-C_6H_4	Ph	**3.50**	75	73 (*S*)
7	1-naphthyl	Ph	**3.48**	40	99 (*S*)
8	1-naphthyl	Ph	**3.50**	32	51 (*S*)
9	2-furyl	Ph	**3.48**	47	87 (*S*)
10	2-furyl	Ph	**3.50**	54	75 (*S*)
11	4-Br-C_6H_4	Ph	**3.48**	16	89 (*S*)
12	4-Br-C_6H_4	Ph	**3.50**	30	87 (*S*)
13	4-Cl-C_6H_4	Ph	**3.48**	10	83 (*S*)
14	4-Cl-C_6H_4	Ph	**3.50**	14	81 (*S*)
15	Ph	4-Me-C_6H_4	**3.48**	88	87 (*R*)
16	Ph	4-Me-C_6H_4	**3.50**	80	87 (*R*)

17	Ph	4-OMe-C_6H_4	**3.48**	60	68 (*R*)
18	Ph	4-OMe-C_6H_4	**3.50**	85	76 (*R*)
19	Ph	1-naphthyl	**3.48**	n.p.	/
20	Ph	1-naphthyl	**3.50**	n.p.	/
21	Ph	4-Cl-C_6H_4	**3.48**	n.p.	/
22	Ph	4-Cl-C_6H_4	**3.50**	n.p.	/

Moderate to excellent *ee*'s (51-99%) were obtained in the arylation of differently substituted *N*-tosylarylimines, containing either electron-donating or electron-withdrawing substutents, while the catalytic efficiency was moderate in most cases, as witnessed by the conversions. An excellent *ee* (99%; entry 7) was obtained with *N*-tosyl-1-naphthaldehyde imine using ligand **3.48**, while only a moderate enantioselectivity (*ee* = 51%; entry 8) was observed with ligand **3.50**. Electron-rich substrates gave generally higher yields (entries 1-10), while a slower addition reaction, associated with lower overall yields, occurred with electron-poor substrates (entries 11-14). Electron-rich arylboronic acids (entries 15-18) gave generally good yields in the addition to *N*-tosylbenzaldimine, associated with moderate/good *ee*'s. The steric hindered group 1-naphthyl on the boronic acid didn't afford the product (entries 19-20), and also the electron-poor arylboronic acid (4-Cl-C_6H_4)$B(OH)_2$ showed a complete inactivity (entries 21-22) as reported in many papers.

5.3. Experimental section

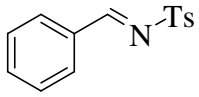
General procedure for the synthesis of *N*-tosyl arylimines[14]

In a flask flushed with nitrogen p-toluensulfonamide (1.1 eq, 4.2 mmol, 754 mg) was suspended in 20 mL of dry CH_2Cl_2. The aromatic aldehyde (1 eq, 4 mmol) was added and finally trifluoroacetic anhydride (1.1 eq, 4.2 mmol, 620 μL). The mixture was heated to reflux (it becomes a solution) and stirred at this temperature for 3 days.

The still warm mixture was poured into 60 mL of water, the aqueous phase was extracted twice with CH_2Cl_2 and the combined organic extracts washed with brine. The solvent was evaporated affording a solid which was purified by flash chromatography using as eluent a mixture of CH_2Cl_2/petroleum ether.

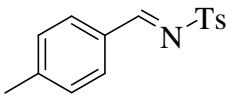
For the characterization of *N*-tosyl arylimines different literature procedures were followed. [15]

Phenyl *N*-tosyl imine



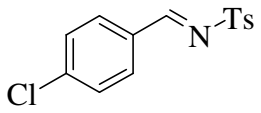
95% yield; ^{1}H NMR (CDCl3) δ 9.03 (s, 1H), 7.87–7.95 (m, 4H), 7.59–7.64 (m, 1H), 7.46–7.52 (m, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 2.44 (s, 3H).

4-Methylphenyl *N*-tosyl imine



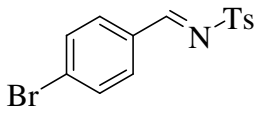
83% yield; ^{1}H NMR (CDCl3) δ 8.98 (s, 1H), 7.86–7.91 (m, 2H), 7.79–7.84 (m, 2H), 7.31–7.34 (m, 2H), 7.27–7.31 (m, 2H), 2.43 (s, 3H), 2.42 (s, 3H).

4-Chlorophenyl *N*-tosyl imine



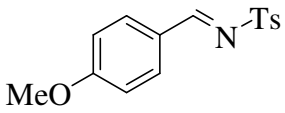
65% yield; ^{1}H NMR (CDCl3) δ 8.99 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.86 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 2.44 (s, 3H).

4-Bromophenyl *N*-tosyl imine



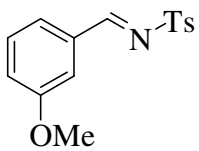
55% yield; ^{1}H NMR (CDCl3) δ 8.97 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 2.44 (s, 3H).

4-Methoxyphenyl *N*-tosyl imine



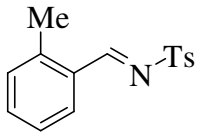
^{1}H NMR (CDCl3) δ 8.94 (s, 1H), 7.85-7.89 (m, 4H), 7.30-7.34 (m, 2H), 6.95-6.98 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H), 2.43 (s, 3H).

3-Methoxyphenyl *N*-tosyl imine



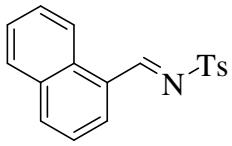
64% yield; ^{1}H NMR (CDCl3) δ 8.99 (s, 1H), 7.87–7.91 (m, 2H), 7.43–7.49 (m, 2H), 7.37–7.42 (m, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.13–7.18 (m, 1H), 3.84 (s, 3H), 2.44 (s, 3H).

2-Methylphenyl *N*-tosyl imine



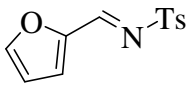
63% yield; ^{1}H NMR (CDCl3) δ 9.34 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.87–7.91 (m, 2H), 7.44–7.49 (m, 1H), 7.32–7.36 (m, 2H), 7.24–7.30 (m, 2H), 2.60 (s, 3H), 2.43 (s, 3H).

1-Naphthyl *N*-tosyl imine



63% yield; ^{1}H NMR (CDCl3) δ 9.62 (s, 1H), 8.98-9.01 (d, *J* = 8.7 Hz, 1H), 8.09-8.18 (m, 2H), 7.92-7.96 (m, 3H), 7.56-7.71 (m, 3H), 7.34-7.37 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H),

2-Furyl *N*-tosyl imine



72% yield; ^{1}H NMR (CDCl3) δ 9.08 (s, 1H), 7.86 (m, 2H), 7.74 (m, 1H), 7.34 (m, 3H), 6.64 (m, 1H), 2.42 (s, 3H).

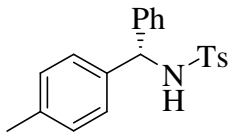
General procedure for the arylation of *N*-tosyl arylimines[9]

In a flame dried Schlenk tube flushed with nitrogen, 1.2 mg (4.65 μmol, 3 mol%) of Rh(acac)(C_2H_4)$_2$ and 9.30 μmol (6 mol%) of the ligand were dissolved in dry dioxane (0.75 mL). After stirring for 30 min at room temperature, 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 water (3 mL)

and extracted with CH_2Cl_2 (3 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue was purified by flash chromatography on silica gel with a mixture of *n*-hexane/EtOAc affording the *N*-tosyl-diarylmethylamine as a white solid.

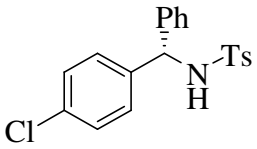
Both the *ee*'s and the absolute configurations were determined by HPLC using a Chiralcel OD-H or AD-H column.[8]

(*S*)-*N*-[(4-Methylphenyl)phenylmethyl]-4-methylbenzenesulfonamide.



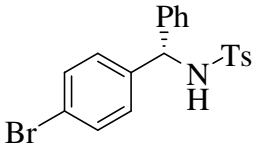
White solid, m.p. 114-116 °C. $[\alpha]_D^{20}$ = -11.0 (*c* 0.7, $CHCl_3$), [HPLC conditions: Chiralcel OD-H column, hexane/2-propanol = 95:5, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 17.5 min for (*S*)-enantiomer, t_R = 25.9 min for (*R*)-enantiomer]. ^{1}H NMR δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.20–7.08 (m, 7H), 7.02–6.95 (m, 4H), 5.52 (d, *J* = 6.8 Hz, 1H), 5.02 (d, *J* = 6.8 Hz, 1H), 2.37 (s, 3H), 2.27 (s, 3H).

(*S*)-*N*-[(4-Chlorophenyl)phenylmethyl]-4-methylbenzenesulfonamide.



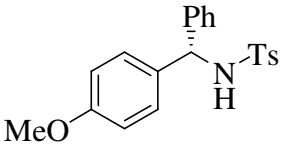
White solid, m.p. 120-122 °C. $[\alpha]_D^{20}$ = -4.8 (*c* 0.97, $CHCl_3$), [HPLC conditions: Chiracel OD-H column, hexane/2-propanol = 93:7, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 18.8 min for (*S*)-enantiomer and t_R = 26.7 min for (*R*)-enantiomer]. ^{1}H NMR δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.22–7.11 (m, 7H), 7.02–7.06 (m, 4H), 5.53 (d, *J* = 6.4 Hz, 1H), 5.41 (br s, 1H), 2.38 (s, 3H).

(*S*)-*N*-[(4-Bromophenyl)phenylmethyl]-4-methylbenzenesulfonamide.



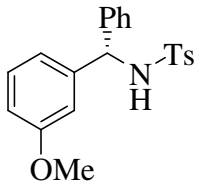
White solid, m.p. 121-123 °C. $[\alpha]_D^{20}$ = -4.1 (*c* 0.81, $CHCl_3$), [HPLC conditions: Chiralcel OD-H column, hexane/2-propanol = 80:20, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 32.0 min for (*S*)-enantiomer, t_R = 44.8 min for (*R*)-enantiomer. ^{1}H NMR δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.22–7.20 (m, 3H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.04–7.02 (m, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 5.51 (d, *J* = 6.8 Hz, 1H), 5.03 (d, *J* = 6.8 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR δ 143.4, 140.0, 139.5, 137.2, 131.5, 129.4, 129.1. 128.7, 127.8, 127.2, 127.1, 121.5, 60.8, 21.5. MS (EI) m/z 415 (M^+). Anal. Calcd for $C_{20}H_{18}BrNO_2S$: C, 57.70; H, 4.36; N, 3.36; Found: C, 58.13; H, 4.10; N, 3.11.

(*S*)-*N*-[(4-Methoxyphenyl)phenylmethyl]-4-methylbenzenesulfonamide.



White solid, m.p. 145-147 °C. $[\alpha]_D^{20}$ = -13.6 (*c* 0.58, $CHCl_3$), [HPLC conditions: Chiralcel OD-H column, hexane/2-propanol = 80:20, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 20.0 min for (*S*)-enantiomer, t_R = 31.7 min for (*R*)-enantiomer]. ^{1}H NMR δ 7.56 (d, *J* = 8.8 Hz, 2H), 7.20–7.18 (m, 3H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.11–7.08 (m, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 5.52 (d, *J* = 6.8 Hz, 1H), 5.03 (br s, 1H), 3.74 (s, 3H), 2.37 (s, 3H).

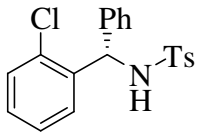
(*S*)-*N*-[(3-Methoxyphenyl)phenylmethyl]-4-methylbenzenesulfonamide.



White solid, m.p. 153-155 °C. $[\alpha]_D^{20}$ = -2.9 (*c* 1.34, $CHCl_3$), [HPLC conditions: Chiralcel OD column, hexane/2-propanol = 95;5, flow = 0.8 mL/min, wavelength = 230 nm, t_R = 29.7 min for (*R*)-enantiomer, t_R = 34.4 min for (*S*)-enantiomer. ^{1}H NMR δ 7.57

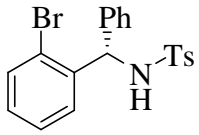
(d, J = 8.8 Hz, 2H), 7.21−7.18 (m, 3H), 7.14−7.09 (m, 5H), 6.73−6.71 (m, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.60 (s, 1H), 5.53 (d, J = 6.8 Hz, 1H), 5.06 (br s, 1H), 3.68 (s, 3H), 2.37 (s, 3H). ^{13}C NMR δ 159.6, 143.1, 142.0, 140.4, 137.4, 129.5, 129.3, 128.5, 127.5, 127.3, 127.2, 119.7, 113.1, 112.9, 61.3, 55.1, 21.4. MS (EI) m/z 367 (M^+). Anal. Calcd for $C_{21}H_{21}NO_3S$: C, 68.64; H, 5.76; N, 3.81; Found: C, 68.45; H, 5.93; N, 3.72.

(*S*)-*N*-[(2-Chlorophenyl)phenylmethyl]-4-methylbenzenesulfonamide.



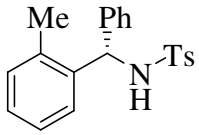
White solid, m.p. 169-171 °C. $[\alpha]_D^{20}$ = +16.5 (c 0.49, $CHCl_3$), [HPLC conditions: Chiralpak AD-H column, hexane/2-propanol = 90:10, flow = 0.7 mL/min, wavelength = 230 nm, t_R = 36.4 min for (*S*)-enantiomer, t_R = 41.8 min for (*R*)-enantiomer]. ^{1}H NMR δ 7.62 (d, J = 8.8 Hz, 2H), 7.35−7.32 (m, 1H), 7.23−7.21 (m, 4H), 7.16−7.14 (m, 4H), 7.06−7.04 (m, 2H), 5.90 (d, J = 6.8 Hz, 1H), 5.22 (d, J = 6.8 Hz, 1H), 2.37 (s, 3H).

(*S*)-*N*-[(2-Bromophenyl)phenylmethyl]-4-methylbenzenesulfonamide.



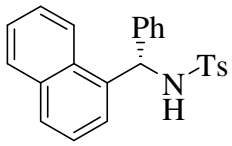
White solid, m.p. 172-174 °C. $[\alpha]_D^{20}$ = +23.3 (c 0.54, $CHCl_3$), [HPLC conditions: Chiralpak AD-H column, hexane/2-propanol = 90:10, flow = 0.7 mL/min, wavelength = 230 nm, t_R = 38.8 min for (*S*)-enantiomer, t_R = 42.8 min for (*R*)-enantiomer]. ^{1}H NMR δ 7.63 (d, J = 7.6 Hz, 2H), 7.43−7.34 (m, 2H), 7.23−7.15 (m, 6H), 7.09−7.04 (m, 3H), 5.91 (d, J = 7.2 Hz, 1H), 5.23 (br s, 1H), 2.37 (s, 3H). ^{13}C NMR δ 143.3, 139.3, 139.1, 137.0, 133.1, 129.5, 129.4, 129.0, 128.6, 127.8, 127.5, 127.4, 127.2, 123.1, 60.5, 21.4; MS (EI) m/z 415(M^+). Anal. Calcd for $C_{20}H_{18}BrNO_2S$: C, 57.70; H, 4.36; N, 3.36; Found: C, 57.93; H, 4.17; N, 3.11.

(*S*)-*N*-[(2-Methylphenyl)phenylmethyl]-4-methylbenzenesulfonamide.



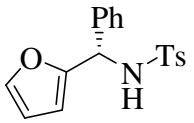
White solid, m.p. 136-138 °C. $[\alpha]_D^{20}$ = +10.0 (*c* 0.98, $CHCl_3$), [HPLC conditions: Chiralcel OD-H column, hexane/2-propanol = 80:20, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 12.0 min for (*R*)-enantiomer, t_R = 15.1 min for (*S*)-enantiomer]. ^{1}H NMR δ 7.54 (d, *J* = 9.2 Hz, 2H), 7.19–7.17 (m, 3H), 7.12–7.09 (m, 4H), 7.06–7.03 (m, 4H), 5.79 (d, *J* = 7.2 Hz, 1H), 5.23 (br s, 1H), 2.35 (s, 3H), 2.15 (s, 3H).

(*S*)-*N*-[(1-Naphthyl)phenylmethyl]-4-methylbenzenesulfonamide.



White solid, m.p. 176-177 °C. $[\alpha]_D^{20}$ = -3.9 (*c* 0.50, $CHCl_3$), [HPLC conditions: Chiralcel OD-H column, hexane/2-propanol = 80:20, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 25.2 min for (*R*)-enantiomer, 32.2 min for (*S*)-enantiomer]. ^{1}H NMR δ 7.85–7.78 (m, 3H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.51–7.36 (m, 4H), 7.30–7.23 (m, 2H), 7.20–7.18 (m, 2H), 7.15–7.12 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.31 (d, *J* = 6.8 Hz, 1H), 5.14 (d, *J* = 6.8 Hz, 1H), 2.35 (s, 3H).

(*S*)-*N*-[(2-Furyl)phenylmethyl]-4-methylbenzenesulfonamide.



Brown solid, m.p. 134-136 °C. $[\alpha]_D^{20}$ = -4.6 (*c* 0.50, $CHCl_3$), [HPLC conditions: Chiralcel OD-H column, hexane/2-propanol = 95:5, flow = 0.8 mL/min, wavelength = 230 nm, t_R = 25.5 min for (*S*)-enantiomer, t_R = 27.8 min for (*R*)-enantiomer]. ^{1}H NMR δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.25–7.22 (m, 5H), 7.18–7.14 (m, 5H), 5.61 (d, *J* = 7.2 Hz, 1H), 5.12 (d, *J* = 7.2 Hz, 1H), 2.37 (s, 3H).

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.[16]

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[1] Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976.

[2] Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, 41, 3692.

[3] Hayashi, T.; Kawai, M.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2004**, 43, 6125.

[4] Cabello, N.; Kizirian, J. C.; Alexakis, A. *Tetrahedron Lett.* **2004**, 45, 4639.

[5] Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128.

[6] Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092.

[7] Tokunaga, N.; Otumaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, 126, 13584.

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

[9] Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976.

[10] (a) Monti, C.; Gennari, C.; Piarulli, U. *Tetrahedron Lett.* **2004**, *45,* 6859. (b) Monti, C.; Gennari, C.; Piarulli, U.; de Vries, J. G.; de Vries, A. H. M.; Lefort, L. *Chem. Eur. J.* **2005**, *11*, 6701.

[11] (a) Monti, C.; Gennari, C.; Piarulli, U. *Chem. Commun.* **2005**, 5281. (b) Monti, C.; Gennari, C.; Piarulli, U. *Chem. Eur. J.* **2007**, *13*, 1547.

[12] Recently, Trost and co-workers reported the successful use use of ligand **26**-$P(O)_2N$ in the palladium-catalyzed asymmetric [3 + 2] trimethylenemethane cycloaddition reactions: Trost, B. M.; Stambuli, J. P.; Silverman, S. M.; Schwörer, U. *J. Am. Chem. Soc.* **2006**, *128*, 13328.

[13] Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56,* 2865.

[14] Lee, K. Y.; Lee, C. G.; Kim, J. N. *Tetrahedron Letters* **2003**, 44, 1231-1234.

[15] (a) Vishwakarama, L. C.; Stringer, O. D.; Davis, F. A. *Organic Syntheses* **1987**, *66*, 203. (b) Brain, E. L.; Prasad, S. R.; Thomas, C. W. *Synlett* **1994**, 493. (c) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75.

[16] Vedejs, E.; Lin, S. *J. Org. Chem.* **1994**, *59*, 1602.