Chiral Bis(*N*-tosylamino)phosphine- and TADDOL-Phosphite-Oxazolines as Ligands in Asymmetric Catalysis

Robert Hilgraf, Andreas Pfaltz*

Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland
Fax +41-61 267-1103; E-mail: pfaltz@ubaclu.unibas.ch

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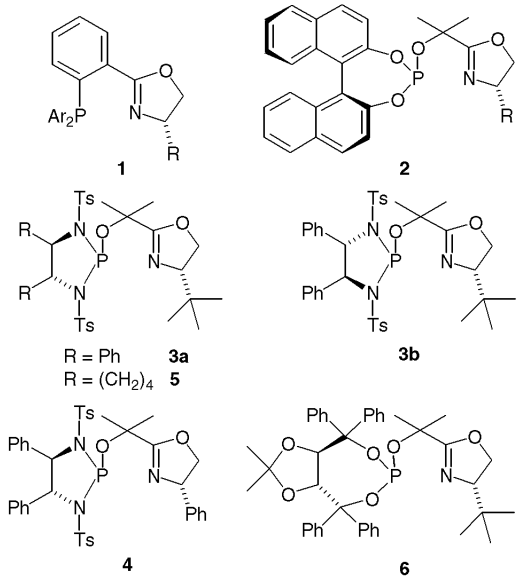
Abstract: A series of *P,N*-ligands containing a chiral oxazoline ring and a chiral bis(*N*-tosylamino)phosphine group derived from a 1,2-diamine or a chiral cyclic phosphite group derived from TADDOL has been prepared. These compounds proved to be efficient ligands for enantiocontrol of palladium-catalyzed allylic alkylations and iridium-catalyzed hydrogenations of olefins.

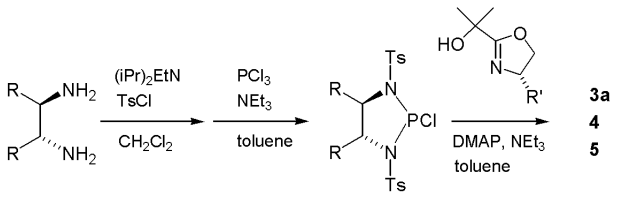
Key words: asymmetric catalysis, chiral *P,N*-ligands, allylic alkylation, Ir-catalyzed hydrogenation

In the course of our studies of enantioselective palladium-catalyzed allylic alkylation,[1-3] we have developed chiral oxazoline-phosphite ligands of type **2**[3] as a new variant of the phosphinooxazoline (PHOX) ligands **1**.[2,4] Although, originally, these ligands were designed specifically for enantio- and regiocontrol in allylic alkylation with 1- and 3-monosubstituted allyl systems, they have also given promising results in the enantioselective 1,4-addition of organozinc reagents to cyclic enones.[5]

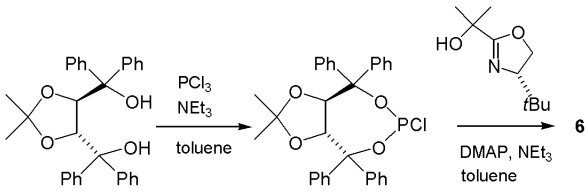


Here, we describe the synthesis and application of the related ligands **3**-**5**, containing a bis(*N*-tosylamino)phosphine group derived from a chiral 1,2-diamine, and ligand **6**, possessing a TADDOL-derived phosphite unit. Analogous TADDOL-based ligands containing either an (*R*)- or (*S*)-4-isopropyloxazoline ring have been reported recently by Heldmann and Seebach.[6] They found that rhodium complexes of these ligands are efficient catalysts for the enantioselective hydrosilylation of ketones.

The synthesis of ligands **3**-**5** was commenced from the readily available enantiomerically pure diamines 1,2-diphenylethylene-diamine and 1,2-diaminocyclohexane. Reaction with tosyl chloride in the presence of diisopropylethylamine in CH_2Cl_2 gave the corresponding bistosylated amines in good yields.[7] Treatment with PCl_3 and triethylamine afforded the bis(*N*-tosylamino)phosphorochloridites as pale yellow solids, which were characterized by mass spectroscopy. Because of their moisture- and air sensitivity these intermediates were converted directly to the desired *P,N*-ligands **3**-**5** by reaction with the oxazoline alcohol, DMAP and triethylamine. Since all attempts to purify the products by column chromatography failed, the crude products were recrystallized from chloroform/hexane. The trace amounts of remaining DMAP were then removed by carefully heating (90°C) under high vacuum. This yielded analytically pure *P,N*-ligands **3**-**5** in 60-80% overall yield from the bistosylated amines.



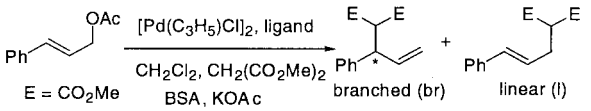
By this route, a wide variety of different derivatives with the structural motif of ligands **3**-**5** should be readily accessible. The modular construction of these ligands allows independent structural variation of the oxazoline ring, the backbone, the sulfonamide groups and the substituents on the diazaphospholidine ring. Although the two stereogenic centers derived from the 1,2-diamine are too far away from the *P*-atom to directly influence a reaction taking place at a *P*-bound metal, they are expected to induce a chiral non-planar arrangement of the TsN-P-NTs unit, resulting in a chiral environment near the coordination sphere of the ligand. Therefore, both the oxazoline and the diazaphospholidine ring are expected to have a distinct effect on the enantioselectivity of a metal-catalyzed process.

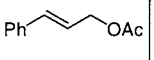
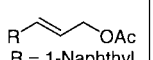
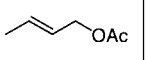
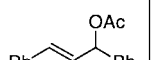
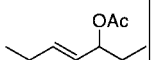
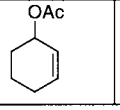


The TADDOL-derived ligand **6** was synthesized in a similar way to the bis(*N*-tosylamino)phosphine ligands **3**-**5**. (*R*,*R*)- or (*S*,*S*)-TADDOL[8] was treated with PCl_3 in the presence of triethylamine to give the phosphorochloridite which was converted directly to ligand **6** by reaction with the oxazoline alcohol, DMAP and triethylamine. Purification by recrystallisation from chloroform/hexane afforded the *P*,*N*-ligand **6** in 71% overall yield.

With these ligands in hand, we evaluated their scope in the Pd-catalyzed allylic alkylation of various substrates (Table 1). Of special interest were the aryl-allyl derivatives (Entries 1-2) because of the promising results obtained previously with ligand **2** (R = *t*Bu).

Table 1 Enantioselective Pd-catalyzed allylic alkylation[a)]



Entry	Substrate	Ligand	%conv[b)]	%ee[c)]	br/l
1		**3a**	100	94 (*S*)	84:16
		4	100	89 (*S*)	38:62
		5	100	95 (*S*)	60:40
		6	100	87 (*S*)	26:74
2	 R = 1-Naphthyl	**3a**	100	98 (*S*)	98:2
		4	100	85 (*S*)	93:7
		5	100	99.4 (*S*)	93:7
		6	100	94 (*S*)	66:34
3		**3a**	100	60 (*S*)	55:45
		4	100	4 (*S*)	64:36
		5	100	50 (*S*)	26:74
		6	100	23 (*S*)	38:62
4		**3a**	100	60 (*S*)	
		4	100	88 (*S*)	
		5	100	52 (*S*)	
		6	100	20 (*S*)	
5		**3a**	53	20	
		4	100	20	
		5	100	9	
		6	100	61	
6		**3a**	100	71 (*R*)	
		4	49	53 (*R*)	
		5	100	1	
		6	100	46 (*R*)	

a) All reactions were carried out with 1 mol% of $[Pd(C_3H_5)Cl]_2$ and 2.5 mol% of ligand in CH_2Cl_2 at r.t. for 20 h (exp. procedure see ref. 11). b) Determined by GC. The yields of the pure products were 85–95% (100% conv.). c) Determined by GC or HPLC using chiral columns.

In comparison to oxazoline-phosphite ligands of type **2**, the new bis(*N*-tosylamino)phosphine-derived ligands **3**-**5** gave comparable or better results in terms of enantio- and regioselectivity in most cases. In particular, ligand **3a** proved to be very effective for regio- and enantiocontrol in reactions of 3-aryl-2-propenyl acetates. The TADDOL-derived ligand **6** gave inferior results with one exception (Entry 5). In the case of (*E*)-3-phenyl-2-propenyl acetate (Entry 1), ligand **3a** gave distinctly higher enantio- and regioselectivities than the phosphite-oxazoline **2** (R = *t*Bu) (94 *vs* 86% *ee*; 84:16 *vs* 69:31). As with ligands of type **2**, the *tert*-butyloxazoline derivative **3a** was superior to the phenyl-substituted analogue **4**. Ligand **5**, containing cyclohexanediamine as the chiral backbone afforded even better enantioselectivities than ligand **3a** in two cases (Entries 1 and 2) but with lower regioselectivity.

Using (1'-naphthyl)prop-2-enylacetate as substrate (Entry 2), ligand **3a** again gave significantly higher enantio- and regioselectivity than BINOL-derived ligands **2** (R = *t*Bu: 95% *ee*, 90:10) or other Pd catalysts reported in the literature.[3] As expected, the *ee*'s and regioselectivities with 2-butenyl acetate (Entry 3) were lower, however ligand **3a** still showed better enantio- and regioselectivity than the phosphite ligands **2** (43% *ee*, 30:70).

With cyclohexenyl acetate (Entry 6), ligand **3a** proved to be superior to the analogous phosphite ligands **2** or phosphinooxazolines **1**. However, the *ee* was still moderate compared to the best values reported so far.[4a,10] In reactions with 1,3-disubstituted acyclic substrates (Entries 4 and 5), all new ligands gave unsatisfactory *ee*'s. Ligand **3b** as well as the corresponding diastereomers of ligands **5** and **6** gave lower *ee*'s and regioselectivities in the reaction of phenylallyl acetate (Entry 1; **3b**: 93% *ee*, 53:47).

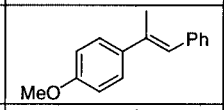
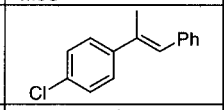
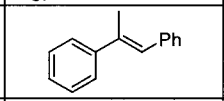
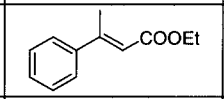
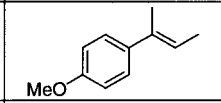
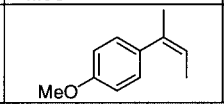
In view of the promising results obtained with phosphinooxazolines **1** in the Ir-catalyzed hydrogenation of olefins,[9] we decided to test our new ligands in this type of reaction (Table 2). The required [Ir(COD)(L)]TFPB complexes (TFPB = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) were readily obtained as air-stable, red-orange crystals by the standard procedure previously reported.[9]

All reactions were carried out with 4 mol% of catalyst at 100 bar hydrogen pressure. Lower catalyst loading or hydrogen pressure resulted in reduced conversions and enantioselectivities. Interestingly, ligand **3b** was more efficient than the diastereomer **3a** in the hydrogenation of (*E*)-1,2-diphenyl-1-propene (Entry 3; 87 *vs* 80% *ee*, 49 *vs* 16% conv.), in contrast to allylic substitution where ligand **3a** gave better results. However, replacement of ligands **5** and **6** by the corresponding diastereomers resulted in lower *ee*'s and conversions.

In comparison to iridium catalysts derived from phosphinooxazolines of type **1**, the novel bis(*N*-tosylamino)phosphine-derived ligands **3b** and **5** gave comparable enantioselectivities but mostly lower conversions. However, in the hydrogenation of ethyl ß-methylcinnamate and (*E*)-2-(4-methoxyphenyl)but-2-ene (Entries 4 and 5), higher *ee*'s than those previously reported were achieved. The TADDOL-derived ligand **6**, in general, gave higher conversions. The best results were achieved in the hydrogenation of (*Z*)-2-(4-methoxyphenyl)but-2-ene (Entry 6),

where the *ee* was improved from 42% (with phosphinooxazolines) to 90% *ee*.

Table 2 Enantioselective hydrogenation of olefins using [Ir(COD)(L)]TFPB catalysts[a)]

Entry	Substrate	Ligand	%conv[b)]	%ee[c)]
1		**3b**	57	92 (*R*)
		5	19	41 (*R*)
		6	98	62 (*R*)
2		**3b**	3	---
		5	4	---
		6	52	78 (*R*)
3		**3b**	49	87 (*R*)
		5	15	94 (*R*)
		6	100	75 (*R*)
4		**3b**	43	86 (*R*)
		5	32	91 (*R*)
		6	100	75 (*R*)
5		**3b**	100	85 (*R*)
		5	65	84 (*R*)
		6	100	76 (*R*)
6		**3b**	100	35 (*R*)
		5	55	42 (*R*)
		6	100	90 (*S*)

a) All reactions were carried out with 4 mol% of catalyst in CH_2Cl_2 at 100 bar H_2 at r.t. for 2 h (exp. procedure see ref. 9). b) Determined by GC. Only one peak could be detected. c) Determined by GC or HPLC using chiral columns.

Our results show that the new *P*,*N*-ligands described above can induce high enantioselectivities in Pd- and Ir-catalyzed reactions, in some cases surpassing the selectivities obtained with phosphinooxazolines or other ligands. In view of the many applications that have been reported for phosphinooxazolines, it will be worthwhile exploring the potential of bis(*N*-tosylamino)phosphine- and phosphite-oxazoline ligands for other metal-catalyzed processes.

Experimental procedure

Ligand **3a**: Freshly destilled PCl_3 (152 mg, 1.1 mmol) was added to a solution of NEt_3 (328 mg, 3.24 mmol) in 4.8 ml of toluene at –78 °C under argon, followed by dropwise addition, *via* a dropping funnel, of a suspension of (1*R*,2*R*)-1,2-N,N'-bis(p-toluenesulfonylamino)-1,2-diphenylethane[7] (400 mg, 0.77 mmol) in 10.4 ml of toluene. The dropping funnel was washed with 4 ml of toluene. The mixture was allowed to slowly warm up to r.t. overnight. After filtration under argon and evaporation of the solvent, the residue was dissolved in 19 ml of toluene, cooled to –78 °C and stirred for 5 minutes. A solution of NEt_3 (784 mg, 7.74 mmol) and DMAP (96 mg, 0.78 mmol) in 8 ml of toluene was added dropwise over 20 minutes, followed by a solution of (-)-(*S*)-2-[1'-hydroxy-1'-methylethyl]-4-*tert*-butyloxazoline[12] (141 mg, 0.76 mmol) in 4 ml of toluene. The mixture was slowly warmed to r.t. overnight. After filtration under argon and evaporation of the solvent, the crude product was recrystallized from anhydrous chloroform/hexane. Traces of DMAP were removed at 90°C/0.01 mbar to yield 400 mg (71 % yield) of analytically pure **3a** as a white solid.

^{1}H NMR: δ ($CDCl_3$) 0.90 (s, 9H), 1.88 (s, 6H), 2.24 (s, 3H), 2.34 (s, 3H), 3.90 (m, 1H), 4.21 (m, 2H), 4.61 (d, *J*=8.2 Hz, 1H), 4.84 (d, *J*=8.3 Hz, 1H), 6.84-7.55 (m, 18H). ^{31}P NMR: δ ($CDCl_3$) 121.25. Anal. calc. for $C_{38}H_{44}N_3O_6PS_2$: C 62.19, H 6.04, N 5.73; found C 62.08, H 6.09, N 5.66.

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