P,N Ligands

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A Mild Dihydrobenzooxaphosphole Oxazoline/Iridium Catalytic System for Asymmetric Hydrogenation of Unfunctionalized Dialins**

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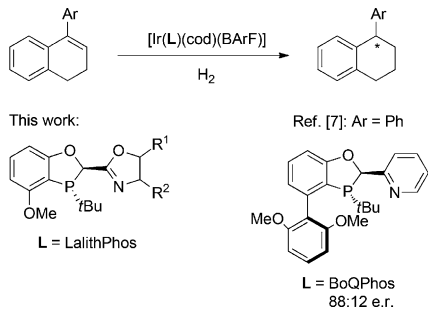
Abstract: *Air-stable P-chiral dihydrobenzooxaphosphole oxazoline ligands were designed and synthesized. When they were used in the iridium-catalyzed asymmetric hydrogenation of unfunctionalized 1-aryl-3,4-dihydronaphthalenes under one atmosphere pressure of H_2, up to 99:1 e.r. was obtained. High enantioselectivities were also observed in the reduction of the exocyclic imine derivatives of 1-tetralones.*

Substituted tetralins,[1] especially those containing stereogenic centers, have been widely utilized in the design and synthesis of biologically active compounds.[2] Recently we were interested in an efficient synthetic route to a family of chiral, unfunctionalized 1-aryl-substituted tetralins in an optically pure form (Scheme 1). One of the most direct approaches would involve the asymmetric hydrogenation of the corresponding dialin precursors. However, the enantioselective hydrogenation of unfunctionalized alkenes has proven to be highly challenging, as there are no coordination groups to complex with the metal center to provide a secondary interaction to position the substrate for enantiofacial discrimination.[3] In particular, cyclic unfunctionalized dihydronaphthalenes are known to be difficult substrates and the current literature methods often require high pressures, and very few dialin substrates have been reported.[4] Buchwald and co-workers reported the titanocene-catalyzed asymmetric hydrogenation of unfunctionalized olefins under high H_2 pressures (up to 136 atm) over long reaction times.[5] More recently Pfaltz and co-workers demonstrated that chiral P,N ligands, when complexed with iridium, can reduce certain cyclic unfunctionalized dihydronaphthalenes with good to high enantioselectivities.[6] Again, this catalytic system generally required 50 atm of pressure of H_2 and was applied to only a handful of substrates. To develop a scalable and economical synthesis of our target molecules, a mild and reactive catalytic system was required. Herein, we describe our work on the development of a novel ligand series for the asymmetric hydrogenation of unfunctionalized 1-aryl dialins and it proceeds under only one atmosphere of H_2.



Scheme 1. Enantioselective synthesis of 1-aryl tetralins. cod = 1,5-cyclooctadiene.

Recently, we reported the design and synthesis of a series of pyridyl-based BoQPhos ligands and their utility in the asymmetric hydrogenation of unfunctionalized alkenes.[7] As part of the study, we demonstrated that asymmetric hydrogenation of a phenyl-substituted dialin could be achieved with a moderate, yet promising 88:12 e.r. (Scheme 1). In the search for a more stereoselective ligand system, we envisioned the incorporation of a chiral oxazoline motif into the design of our next generation P,N ligands for the hydrogenation of unfunctionalized 1-aryl-3,4-dihydronaphthalenes.

Synthesis of the phosphine oxazoline LalithPhos ligands **5a–f** started with the chiral intermediate **1** (Scheme 2).[8] Deprotonation followed by CO_2(g) afforded the carboxylic acid after a MeOH quench. After generating the diastereomerically pure acid **2**, the amide-coupling products were obtained with various amino alcohols. Both enantiomers of the *cis*-1-amino-2-indanols[9] were integrated into the ligand design, as the conformationally constrained indanyl platform has been shown as a particularly valuable building block in a variety of catalytic processes, thus leading to high levels of asymmetric induction.[10] We anticipated that this bulky and constrained structure could create an effective chirally discriminative environment for the asymmetric hydrogenations. The amides **3b–f** were synthesized with 65–88% yields in the presence of EDC/HOBt. The amide **3a** was obtained with the aid of propylphosphonic anhydride (T_3P)[11] in 72% yield. The subsequent cyclization to the oxazolines **4b–d** was achieved under TsCl/Et_3N conditions. However, for **3a** and the indanol amides **3e** and **3f**, the Lewis acid $BF_3{\cdot}Et_2O$ was required for cyclization.[12] All the amides were isolated in modest to good yields.

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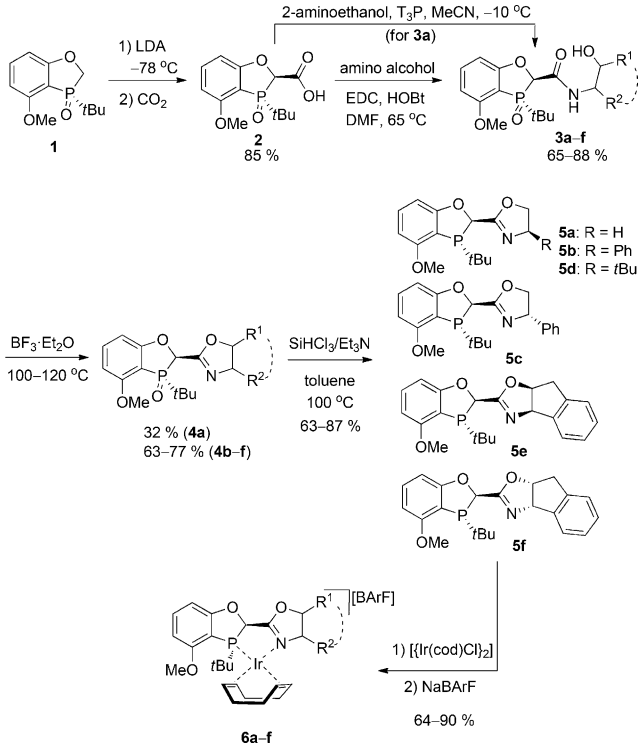
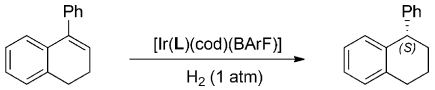


Scheme 2. Synthesis of LalithPhos ligands **5a–f**.[19] DMF = *N*,*N*-dimethylformamide, EDC = 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide, LDA = lithium diisopropylamide.

The reduction of the phosphine oxides **4a–f** provided the desired LalithPhos in 70–85 % yields (Scheme 2).[15] Another set of diastereomeric ligands with the phenyl substituent, **5b** and **5c**, was also prepared to investigate the influence of the relative configuration of the substituent chirality on the oxazoline. No racemization or epimerization of the chiral centers on the phosphorus or the amino alcohols was observed during the phosphine oxide reduction. The corresponding cationic iridium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (BArF) complexes were prepared by complexation with [{Ir(cod)Cl}$_2$] and followed by anion exchange with NaBArF.[16] Both the ligands and the catalysts are stable in air. No detectable oxidations were observed by ^{31}P NMR analysis when the sample was left open air at ambient temperature for more than four weeks.

To test the effectiveness of these new ligands towards asymmetric hydrogenation of 1-aryl-dialins, the iridium complexes **6a–f** (Scheme 2) were used as catalysts for the reduction of 1-phenyl-3,4-dihydronaphthalene to produce enantiomerically enriched 1-phenyltetralin (Table 1). Complete conversion resulted for the catalysts **6a–d** under 1 atm of H_2 pressure. The complexes with different ligands provided dramatically different enantioselectivities. The unsubstituted oxazoline **5a** was not selective at all. The *R*-phenyl-substituted ligand **5b** and the *R*-*tert*-butyl ligand **5d** produced the enantiomeric ratios of 96:4 and 95:5, respectively. The absolute configuration of the major enantiomer was designated as *S*, as determined by the vibrational circular dichroism (VCD) analysis.[17] The diastereomeric ligand **5c** with the *S*-

Table 1: Hydrogenation of 1-phenyl-3,4-dihydronaphthalene.[a]



L	Conv. [%][b]	e.r.[b]
5a	100	49:51
5b	100	96:4[c]
5c	100	99:1 (*R*)[d]
5d	100	95:5
5e	80	89:11
5f	4	58:42

[a] Reactions performed at 23 °C for 20 h using 2 mol % of the catalyst in CH_2Cl_2 unless specified otherwise. [b] Conversions and e.r. values were determined by GC using Chiraldex B-PH 30 m, isothermal 150 °C. [c] Isolated in 90 % yield. [d] Performed at 10 °C. The major enantiomer is *R* configured.

phenyl moiety afforded the product with an increased e.r. value of 99:1 at 10 °C with the opposite chirality. The ligand **5c** is more selective than the phosphine imidazoline ligands reported lately.[18] The catalyst with the aminoindanyl-substituted ligand **5e** produced an 80 % conversion in 89:11 e.r. Surprisingly, the diastereomeric ligand **5f** was ineffective and low conversion was resulted.

The single-crystal X-ray structure of the catalyst **6d**[19] provided insight into the enantiomeric induction in the hydrogenation processes. The DFT calculations on the transition states supported the stereochemical model.[20] The trisubstituted alkene was found to have one viable binding mode to the dihydride iridium complex where the dihydronaphthalene portion of the olefin is positioned in the open quadrant of the iridium complex[21] (Figure 1). This arrangement would in turn position the less sterically demanding side of the alkene with the phenyl substituent in close proximity to the oxazoline substituent of the ligand. In this capacity, the complex **6c** would expose the *Si* face of the alkene for the metathesis hydrogen transfer, thus generating the *R* configuration of the σ-alkyl/iridium intermediate. Furthermore, the

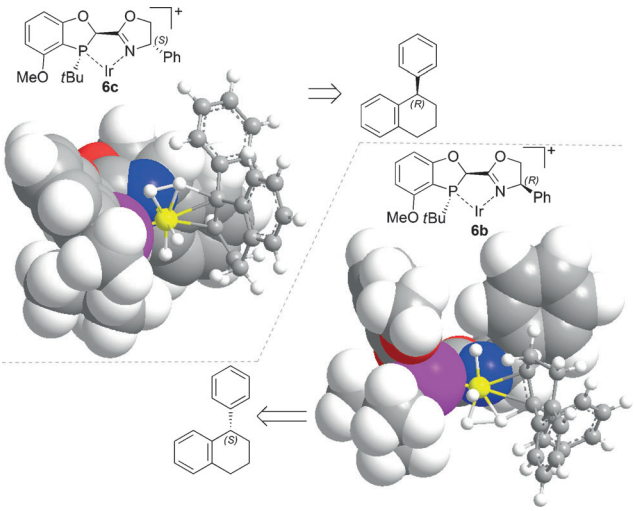


Figure 1. DFT-calculated transition states and stereochemical models.

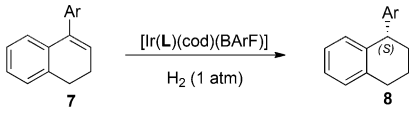
iridium complex **6b** would expose the *Re* face of the alkene for the metathesis hydrogen transfer, thus generating the *S* configuration of the bound intermediate. A fast reductive elimination process would then generate the reduced products with switched enantioselectivity.

1-Aryl-3,4-dihydronaphthalenes with various substituents were then prepared and tested in the hydrogenation reactions (Table 2). The enantioselectivity increased with an *ortho*-tolyl group (**7a**), presumably because of the added steric hindrance. The catalyst with the *tert*-butyl ligand **5d** furnished the adduct **8a** in 99:1 e.r. (entry 1). Catalysts with the ligands **5b**, **5c**, and indanyl **5e** reduced the alkene **7a** with the same enantiomeric ratio of 97:3. Again a reversed enantioselectivity was observed when using the ligand **5c**. The substrate **7b** where *o*-methyl was replaced by an *o*-methoxy group, a slightly compromised e.r. of 90:10 was afforded (entry 2). When the methoxy group is at the *para* position of the phenyl group (**7c**), the selectivity was restored and the adduct **8c** was produced in 98:2 e.r. (entry 3). In comparison, the *para*-chloro adduct **8d** was produced in 95:5 e.r. (entry 4). Low conversion resulted for the alkene **7e** with an *ortho*-methyl ester. The *cis*-aminoindanol-derived ligand **5e** was the most effective, thus producing the adduct **8e** in 98:2 e.r. However, a high pressure was required to observe an 88% conversion (entry 5). The reduced reactivity of the *ortho*-substituted substrates might be due to the potential steric interaction with the catalyst. The unique reactivity of the aminoindanyl ligand **5e** is presumably due to the special ligand structure of the conformationally constrained indane platform. 3,4-Dihydro-1,1′-binaphthalenes are generally challenging to prepare because of the dehydrogenative side reaction to produce binaphthalenes.[22,23] Dihydronaphthalene (**7f**; entry 6) was prepared in 70% yield by Suzuki coupling between 1-naphthyl boronic acid and the corresponding triflate using the BI-DIME ligand. Asymmetric hydrogenation of **7f** provided the chiral 1,2,3,4-tetrahydro-1,1'-binaphthalene **8f** in 99:1 e.r. No dehydrogenated impurity was observed during the reduction. A similar e.r. value of 97:3 was obtained with a halogen group at the 6-position of the dihydronaphthalene **7g** (entry 7). A slightly lower selectivity of 91:9 e.r. was observed with the 6-methoxy substituted **7h** (entry 8). The catalyst is also able to reduce 4-phenylchromene **7i**; the adduct **8i** was afforded in 93:7 e.r. in the presence of the ligand **5c** (entry 9).

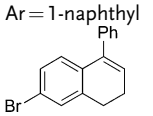
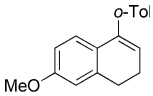
These new catalysts were also used in the preparation of 4-substituted 1-aryl tetralins (Table 3). The dialins **9a**,**b** were prepared in 55–60% yield from (*S*)-4-(3,4-dichlorophenyl)-1-tetralone, a precursor for the synthesis of Sertraline.[1a] With both phenyl and *o*-tolyl substituents at the 1-position, hydrogenation of **9a** and **9b** with the ligand **5c** afforded a greater than 99.5:0.5 d.r. favoring the *cis*-tetrahydronaphthalene **10** (entries 2 and 3). The catalyst with the *trans*-phenyl ligand **5b**, in contrast, produced the *trans*-diastereomer **11a** as the major one in 82:18 d.r.

Encouraged by these results, we further investigated the hydrogenation reaction of related exocyclic ketimines derived from 1-tetralones. A survey of the literature revealed that asymmetric hydrogenation of these exocyclic imines using iridium catalysts generally afforded low enantioselectivities because the conformational strain, upon coordination to iridium, in the transition state caused by the cyclic structures.[24] An encouraging result of iridium-catalyzed enantioselective hydrogenation of ketimines was reported by Ding and co-workers and up to 98% *ee* was achieved with a spirophosphine oxazoline ligand.[25]

Table 2: Hydrogenation of 1-aryl-3,4-dihydronaphthalenes.[a]

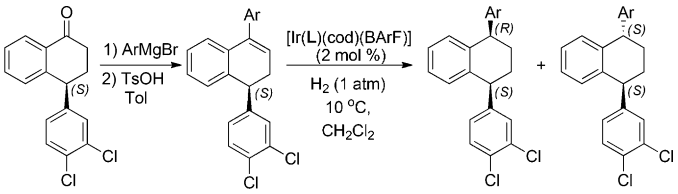


7 8

Entry	Alkene		L	e.r.[b]
1	Ar = 2-MeC_6H_4	**7a**	**5b**	97:3
			5c	97:3 (*R*)
			5d	99:1[c]
			5e	97:3
2	Ar = 2-$OMeC_6H_4$	**7b**	**5d**	90:10
3	Ar = 4-$OMeC_6H_4$	**7c**	**5c**	98:2 (*R*)
4	Ar = 4-ClC_6H_4	**7d**	**5b**	95:5
5	Ar = 2-$CO_2MeC_6H_4$	**7e**	**5e**	98:2[d]
6	Ar = 1-naphthyl	**7f**	**5d**	>99:1
7		**7g**	**5b**	97:3
8		**7h**	**5c**	91:9 (*R*)[c]
9		**7i**	**5c**	93:7 (*R*)

[a] Reactions performed at 10 °C for 20 h using 2 mol% of the catalyst in CH_2Cl_2. [b] Conversions and e.r. were determined by GC or HPLC using a chiral stationary phase. Complete conversions unless specified otherwise. The absolute configuration for the major enantiomer was obtained from VCD analysis. [c] 23 °C. [d] 88% conversion under 55 atm H_2.

Table 3: Hydrogenation of 4-substituted 1-aryl dialins.[a]



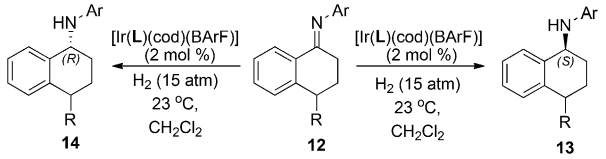
9 10 11

Entry	Ar	L	Conv. [%][b]	d.r.[b]
1	Ph (**9a**)	**5b**	100	18:82
2	Ph (**9a**)	**5c**	100	>99.5:0.5
3	*o*-Tol (**9b**)	**5c**	100	>99.5:0.5

[a] See the Supporting Information for the synthesis of alkene **9**. Hydrogenations performed at 10 °C for 20 h using 2 mol% of the catalyst in CH_2Cl_2. [b] Conversions and d.r. were determined by HPLC using a chiral stationary phase or by ^1H NMR analysis. The *cis*- and *trans*-diastereomers were determined by 2D-NMR analysis. Ts = 4-toluenesulfonyl.

To our delight, the LalithPhos/iridium system showed excellent enantioselectivity towards the exocyclic imine reduction (Table 4). The imine **12a** was successfully reduced by the Ir/**5b** catalyst and the chiral amine adduct **13a** was

Table 4: Hydrogenation of exocyclic N-aryl-dihydronaphthalene ketimines.[a]



Entry	Imine	Ar	R	L	e.r.[b]
1	**12a**	Ph	H	**5b**	97:3 (**13a**)
2	**12b**	*o*-Tol	H	**5b**	>99:1 (**13b**)
3	**12b**	*o*-Tol	H	**5c**	98:2 (**14b**)
4	**12c**	*o*-Tol	(*S*)-3,4-$Cl_2C_6H_3$	**5b**	>99:1 (d.r.) (**13c**)
5	**12c**	*o*-Tol	(*S*)-3,4-$Cl_2C_6H_3$	**5c**	98:2 (d.r.) (**14c**)

[a] Reactions performed at 23 °C for 15 h using 2 mol% of the catalyst in CH_2Cl_2 with complete conversions. [b] Conversions and e.r. (or d.r.) were determined by HPLC using a chiral stationary phase. The *cis*- and *trans*-diastereomers were determined by 2D-NMR analysis.

formed in 97:3 e.r.[26] The enantiomeric ratio was increased to greater than 99:1 for imine **12b** which had an *o*-tolyl substituent on the imine nitrogen atom. Similarly, the enantiomeric amine product **14b** was afforded using the iridium catalyst derived from the ligand **5c**. For the (*S*)-4-(3,4-dichlorophenyl)-substituted ketimine **12c**, which has chirality in the backbone, the asymmetric hydrogenation with the ligand **5b** produced the *cis*-amine **13c** in greater than 99:1 d.r., and the *trans*-amine **14c** in 98:2 d.r. with the ligand **5c**. It is noted that the chiral substituent has little effect on the selectivity, thus indicating a ligand-controlled environment during the asymmetric hydrogenations.

In summary, a series of modular P-chiral dihydrobenzooxaphosphole oxazoline derived Lalithphos ligands were designed and synthesized. By judicious choice of the ligand substituents, both enantiomers of 1-aryltetralins could be produced enantioselectively using the hydrogenation reactions. It is worth noting that the new ligand system has exhibited significantly enhanced reactivity compared to that of known systems which allowed the asymmetric hydrogenation of the challenging unfunctionalized alkenes and exocyclic ketimines under mild reaction conditions. It was shown that the chirality on the oxazoline is crucial for the high enantioselectivity. Further application of these ligands is under investigation.

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[26] The major enantiomer is *S* configured as determined from VCD studies. See the Supporting Information.

