PHOX-based Phosphite-oxazoline Ligands for the Enantioselective Ir-catalyzed Hydrogenation of Cyclic β-enamides

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ABSTRACT: Simple Ir-PHOX-based phosphite-oxazoline catalysts have been successfully applied in the asymmetric hydrogenation of cyclic β-enamides providing better enantioselectivities than previous effective Ru- and Rh-catalysts. This protocol allows the synthesis of 2-aminotetralines and 3-aminochromanes, key structural units found in many therapeutic agents and biologically active natural products, in high chemical yields and enantioselectivities (ee's up to 99%). High enantioselectivities have also been achieved in the hydrogenation of cyclic α-enamides.

KEYWORDS: Hydrogenation, iridium, β-enamides, phosphite-oxazoline ligands, asymmetric catalysis

Enantiomerically pure compounds are of great importance in pharmacy, agro-chemistry, fine chemistry and natural product chemistry. Metal-catalyzed asymmetric transformations are one of the most powerful tools for their preparation. Among them, the asymmetric hydrogenation of prochiral substrates turns out to be one of the most reliable catalytic methods, mainly because of its perfect atom economy, operational simplicity and high efficiency.[1] To date this field has been dominated by Rh-, Ru- and Ir-catalysts. While Rh/Ru-PP based catalysts have been successfully applied to the hydrogenation of a wide range of functionalized substrates,[2] Ir-PN catalysts have been mainly used in the reduction of minimally functionalized olefins.[3] Despite these advances, there are substrates such as cyclic β-enamides whose hydrogenation is still a challenge.

2-Aminotetralines **1** and 3-aminochromanes **2** are key structural units that can be found in numerous therapeutic agents and biologically active natural products. Two representative examples are rotigotine,[4] a dopamine agonist used for the treatment of Parkinson's disease, and alnespirone,[5] a selective 5-HT1A receptor with antidepressant and anxiolytic properties (Figure 1). It is easy to envisage that the asymmetric hydrogenation of β-enamides can be an entry point to the synthesis of these compounds. Nevertheless, in contrast to the α-enamides, most of the catalysts for β-enamides provide low enantiomeric excesses[6] although some successful protocols using Ru- and Rh-based catalysts are available[7]. Among the most successful examples we can mention the Ru-diphosphine catalysts by Ratovelomanana-Vidal *et al.* that reached enantioselectivities up to 96% ee in the reduction of enamides derived from 3-chromanones.[7d] More recently, Tang *et al.* presented the nine-step synthesis of WingPhos, a P-stereogenic diphosphine ligand, that has been applied to a broader number of substrates obtaining high enantioselectivities both for enamides derived from 2-tetralines (ee's up to 96%) and also for enamides derived from 3-chromanones (ee's in the range 94-98%).[7f] The discovery of efficient ligands prepared in a few steps, from simple starting materials, easy to handle (solid, robust and air stable) and modular for the M-catalyzed asymmetric hydrogenation of cyclic β-enamides is still therefore a relevant topic.

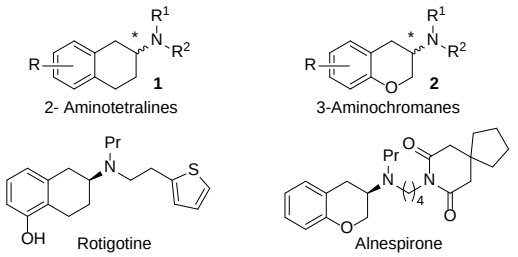


Figure 1. Structure of biologically active compounds containing 2-aminotetraline **1** and 3-aminochromane **2** structural units

Over the last decades, we among others have shown the advantages of introducing a biaryl phosphite moiety in the ligand for several metal-catalyzed asymmetric transformations.[8] In general, the use of biaryl-based phosphite ligands improves both the ligand's efficiency and the substrate scope. The main reason for this behavior is that the biaryl phosphite group is flexible enough to accommodate the chiral pocket of the catalysts to the steric demands of the substrate. It is not surprising therefore that we have recently found that phosphite-based PHOX ligands **L1**-**L3** (Figure 2) can be included in the family of privileged ligands not only because of their ability to control the stereochemistry in a variety of catalytic processes (i.e. asymmetric Pd-catalyzed Heck[9] and allylic substitution[10] reactions, asymmetric Ir-catalyzed hydroboration,[11] …) but also because of their exceptionally broad substrate scope. Moreover, phosphite ligands are attractive for catalysis because they are less sensitive than phosphines to air and other oxidizing agents, they are easy to prepare from commercial alcohols and they are amenable to parallel synthesis. All these features make it easier to prepare large series of ligands in the quest to maximize catalytic performance for each particular reaction and substrate. In this context, we have recently shown the benefits of using heterodonor phosphite-N ligands for the Ir-catalyzed hydrogenation of minimally functionalized olefins,[12] which in the last decades have become the state of art for the asymmetric hydrogenation of these challenging substrates. However, the potential of Ir-PN as catalyst for the asymmetric hydrogenation of functionalized olefins has been overlooked.[13]

In this communication, we report the highly efficient enantioselective synthesis of 2-aminotetralines and 3-aminochromanes through asymmetric Ir-catalyzed hydrogenation of cyclic β-enamides using phosphite-based PHOX ligands **L1**-**L5a**-**c** (Figure 2). Ligands **L4**-**L5** differ from ligands **L1**-**L3** by a methylene spacer between the oxazoline and the phenyl ring of the ligand backbone, and allow studying the

effect of the size of the chelate ring than has been found to influence the catalytic performance in the hydrogenation of several olefins.[14] We have also extended the substrate scope with examples containing cyclic α-enamides that allows the synthesis of the corresponding 1-aminotetralines and 4-aminochromanes.[15]

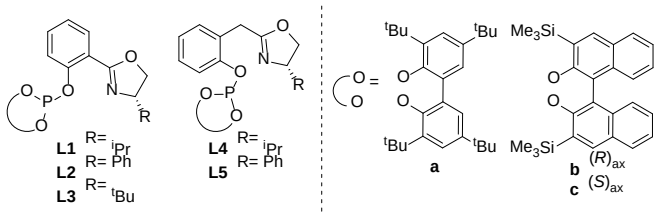
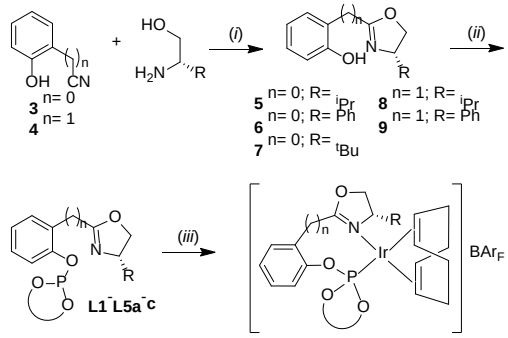


Figure 2. Phosphite–oxazoline ligands **L1**-**L5a**-**c** (all ligands except **L1a** are new)

The synthesis of new Ir-catalyst precursors [Ir(cod)(**L1**-**L5a**-**c**)]BAr_F is straightforward in only three steps from readily available starting materials (Scheme 1). The coupling of hydroxyl-cyanides **3** and **4** with the corresponding amino alcohol afforded the hydroxyl-oxazolines **5**-**9**. The desired diversity in the oxazoline substituent was achieved in this step. Then, condensation of the desired in situ formed phosphorochloridites $ClP(OR)_2$ $(OR)_2$= **a**-**c**) with the corresponding hydroxyl-oxazoline yielded phosphite-oxazoline ligands **L1**-**L5a**-**c**,[16] with different biaryl phosphite groups. All ligands were isolated in high yields as white solids. They were stable in air and very stable to hydrolysis, so further manipulation and storage was performed in air. Finally, complexation of the ligands to $[Ir(\mu\text{-}Cl)(cod)]_2$ followed by in situ Cl^-/BAr_F^- counterion exchange with $NaBAr_F$ gave access to the desired cationic Ir-catalyst precursors. They were isolated in pure form as air-stable red solids in excellent yields after simple extraction. No further purification was required.

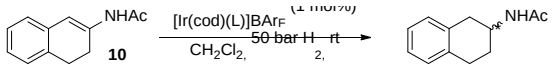


(*i*) $ZnCl_2$, toluene or chlorobenzene at reflux for 18-72 h (yields 62-79%). (*ii*) $ClP(OR)_2$ $(OR)_2$= **a**-**c**, Py, toluene at rt for 18 h (yields 69-80%). (*iii*) $[Ir(\mu\text{-}Cl)(cod)]_2$, CH_2Cl_2 at 40°C for 60 min then H_2O, $NaBAr_F$ at rt for 30 min (yields 89-96%).

Scheme 1. Synthesis of phosphite-oxazoline ligands **L1**-**L5a**-**c** and the corresponding Ir-catalyst precursors

In a first set of catalytic experiments, we explored the hydrogenation of *N*-(3,4-dihydronaphthalen-2-yl)acetamide **10** to study the efficiency of the [Ir(cod)(**L1**-**L5a**-**c**)]BAr_F catalyst precursors (Table 1). **10** was chosen as the model substrate because it had been studied with a wide range of ligands. This enabled the direct comparison with previous results. The hydrogenations were performed under 50 bar of H_2 in dichloromethane at room temperature using 1 mol% of catalyst loading. The effect of the biaryl phosphite group on catalytic performance was studied with ligands **L1a**-**c**. We found a cooperative effect between the configurations of the biaryl phosphite group and of the oxazoline. The presence of a chiral *R*-biaryl phosphite moiety is therefore necessary to maximize enantioselectivities and activities (entry 2 vs 1 and 3). These results also indicated that the PHOX-ligand backbone is not able to control the tropoisomerism of the biphenyl phosphite moiety (**a**). Comparing the results of ligands **L1**-**L3b** it can be seen that the nature of the oxazoline substituent has an important impact on catalytic performance. The presence of a *tert*-butyl oxazoline group led to low activity and enantioselectivity (entry 5). The best activity and enantioselectivity were obtained with ligand **L2b** (entry 4) which contains a phenyl oxazoline moiety. This turned to be economically advantageous because (*S*)-phenylglycinol is the less expensive of the three amino alcohols used (eight times cheaper than *tert*-leucinol used in ligand **L3**). Interestingly, the introduction of a methylene spacer between the oxazoline and the phenyl ring (with phosphite-oxazoline ligands **L4** and **L5**) had a positive effect on enantioselectivity. Both ligands **L4b** and **L5b** provided the hydrogenated product in full conversion and in 98% ee (entries 6 and 7). Finally, the hydrogenation of **10** by using the related phosphine-oxazoline PHOX-Ph ligand **11** provided lower conversion and enantioselectivities under the same reaction conditions (Table 1, entry 8 vs 4 and 7). This result confirms the positive effect of introducing a binaphtyl phosphite moiety into the ligand design. Interestingly, the catalytic performance is maintained regardless the hydrogen pressure. So, full conversion and excellent enantioselectivities were also achieved at 10 bar of H_2 (entry 9).

Table 1. Asymmetric hydrogenation of 10 using [Ir(cod)(L1-L5a-c)]BAr_F[a]



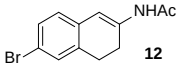
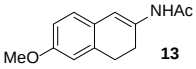
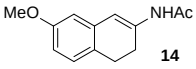
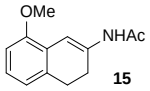
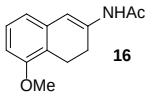
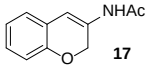
Entry	Ligand	% Conv[b]	% ee[c]
1[d]	**L1a**	75	30 (*S*)
2	**L1b**	80	92 (*S*)
3[d]	**L1c**	56	50 (*R*)
4	**L2b**	95	96 (*S*)
5	**L3b**	30	30 (*S*)
6	**L4b**	100	98 (*S*)
7	**L5b**	100	98 (*S*)
8	 **11**	58	72 (S)
9[e]	**L5b**	100	98 (*S*)

[a] Reactions were run at 23 °C with [Ir(cod)(**L1**-**L5a**-**c**)]BAr_F (1 mol%), **10** (0.5 mmol), CH_2Cl_2 (2 mL) for 20 h. [b] Conversions were measured by ^1H NMR spectroscopy. [c] Enantiomeric excess determined by chiral HPLC. [d] Full conversions achieved after 48 h. [e] Reaction carried out at 10 bar of H_2.

To further study the behavior of [Ir(cod)(**L4b**)]BAr_F and [Ir(cod)(**L5b**)]BAr_F catalyst precursors, we first extended our work to the hydrogenation of other cyclic β-enamides. Table 2 shows the results using catalysts Ir/**L5b** that had provided, together with Ir/**L4b**, the best results in the asymmetric hydrogenation of **10** (for a full set of results see Table S1 in the Supporting Information). We were pleased to discover that [Ir(cod)(**L5b**)]BAr_F catalytic system is very tolerant to

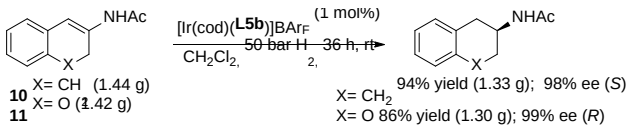
variations in the substitution pattern of the fused benzene ring. Thus, a range substituted cyclic β-enamides derived from β-tetralones were hydrogenated in high yields and with excellent enantioselectivities (ee's ranging from 97% to 99%; entries 1-5) comparable to those achieved with substrate **10**. Among them, it should be denoted the excellent result with (5-methoxy-3,4-dihydronaphthalen-2-yl)acetamide **16** (entry 5), whose hydrogenated product is a key intermediate for the synthesis of rotigotine. Also interesting is the almost perfect enantioselectivity (99% ee, entry 6) and moderate yield achieved in the hydrogenation of *N*-(2H-chromen-3-yl)acetamide **17**, which provides the crucial intermediate for the synthesis of alnespirone. Finally, we extended the substrate scope to the hydrogenation of α-enamides. We found that Ir-**L5b** catalyst precursor is also able to successfully hydrogenate *N*-(3,4-dihydronaphthalen-1-yl)acetamide **18** and *N*-(2H-chromen-4-yl)acetamide **19** in high enantioselectivities (ee's up to 96%, entries 7 and 9).

Table 2. Asymmetric hydrogenation of cyclic α- and β-enamides using [Ir(cod)(L5b)]BAr$_F$[a]

Entry	Substrate	% Conv (% Yield)[b]	% ee[c]
1	 **12**	100 (79)	98 (*S*)
2	 **13**	100 (89)	98 (*S*)
3	 **14**	100 (88)	99 (*S*)
4	 **15**	100 (91)	99 (*S*)
5	 **16**	100 (90)	97 (*S*)
6	 **17**	75 (62)	99 (*R*)
7[d]	 **18**	99 (88)	95 (*R*)
8[d]	 **19**	70 (63)	96 (*R*)

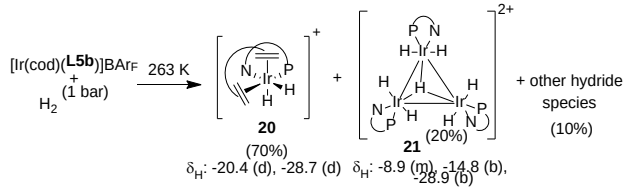
[a] Reactions were run at 23 °C with [[Ir(cod)(**L5b**)]BAr$_F$ (1 mol%), substrate (0.5 mmol), H_2 (50 bar), CH_2Cl_2 (2 mL) for 20 h. [b] Conversions were measured by ^{1}H NMR spectroscopy. [c] Enantiomeric excess determined by chiral HPLC. [d] Reactions carried out at 10 bar of H_2.

The practical applicability of Ir-**L5b** catalytic system is demonstrated by performing the asymmetric hydrogenation of *N*-(3,4-dihydronaphthalen-2-yl)acetamide **10** and *N*-(2H-chromen-3-yl)acetamide **17** at 7.5 mmol scale, affording the desired hydrogenated products *N*-(1,2,3,4-tetrahydronaphthalen-2-yl)acetamide in 94% yield and 98% ee; and *N*-(chroman-3-yl)acetamide in 86% yield and 99% ee (Scheme 2).



Scheme 2. Practical synthesis using Ir-**L5b** catalyst precursors

The asymmetric hydrogenation of minimally functionalized olefins and imines using Ir-P,N ligands is known to proceed via Ir(III)/Ir(V) mechanisms,[3,17] in which the minor isomer reacts faster to provide the major hydrogenated product.[18] In the case of enamides it is feasible that they bind as bidentated to the Ir-center, being the alkene *trans* to the phosphite moiety. However, the possibility that the mechanism proceeds via Ir(I)/Ir(III) intermediates like the Rh-catalysts could not be excluded.[7e,19] To gain further insight into the preferred reaction pathway, we first studied the oxidative addition of H_2 to [Ir(cod)(**5b**)]BAr$_F$ precursor by bubbling H_2 in a CD_2Cl_2 solution at 263 K (Scheme 3). Two major species together with several minor species were observed. All of them have small phosphorus-hydride coupling constants ($^2J_{P\text{-}H} \leq 32$ Hz) in common that indicate that all the hydrides are *cis* to the phosphorus atom. The two major species have been attributed to one of the two possible [Ir(H)$_2$(cod)(**L5b**)]BAr$_F$ (**20**) and to the catalytically inactive trinuclear iridium hydrido species [Ir$_3$(μ$_3$-H)(H)$_6$(**L5b**)$_3$](BAr$_F$)$_2$ (**21**)[20]. We next investigated the reactivity of iridium precatalysts [Ir(cod)(**L5b**)]BAr$_F$ with H_2 (50 bar) in the presence of enamide **14**. The HPNMR study under hydrogenation conditions in CD_2Cl_2 proved to be difficult due to the high reactivity and multifaceted aggregation behavior of Ir-hydride species. The VT-NMR spectra indicated a complex mixture of hydride species, which evolve over time (see Supporting Information). Thus, we have been able to detect an Ir-hydride intermediate, with the hydride signals as double doublets at -28.8 and -19.1 ppm. This intermediate disappears upon depletion of the substrate which suggests that it could be attributed to an hydride intermediate with the substrate coordinated. However, the major intermediates correspond to hydride species that remain even after the hydrogenation of the substrate has been completed. This fact together with the absence of signals corresponding to [Ir$_3$(μ$_3$-H)(H)$_6$(**L5b**)$_3$](BAr$_F$)$_2$, suggests that they can be attributed to Ir-hydride species with the hydrogenated product coordinated. All these data do not therefore provide a clear indication of the type of mechanism involved. Further studies to find an experimental protocol to control the formation of Ir-hydride species in CD_2Cl_2 are required. A detailed experimental/computational study is therefore necessary to clearly identify the preferred reaction pathway.



Scheme 3. Oxidative addition of H_2 to [Ir(cod)(**L5a**)]BAr$_F$ complex

In conclusion, we have shown the enantioselective hydrogenation of cyclic β-enamides using novel Ir-catalysts modified with phosphite-based PHOX ligands that provide better enantioselectivities than Ru- and Rh-catalysts described in the literature. This new protocol allows the synthesis of 2-aminotetralines and 3-aminochromanes in high chemical yields and enantioselectivities (ee's up to 99%). Advanta-

geously, the new Ir-catalysts have been easily prepared in only 3 steps from readily available sources. Another advantage over previous ligands is that the new ligands are stable to air and therefore easier to handle, manipulate and store. We found an important effect of the size of the chelate ring on enantioselectivity. Enantioselectivities obtained with ligands **L4**-**L5**, which form a seven-membered chelate ring, were higher than with ligands **L1**-**L3**. Interestingly, the reactions could be performed at low hydrogen pressure with no loss of selectivity. We have also extended the substrate scope with examples containing cyclic α-enamides. Application to the synthesis of other biologically active compounds and a detailed mechanistic study is currently under way.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interests.

Supporting Information

Experimental procedures for the preparation of ligands and Ir-complexes and their characterization details; experimental procedure for the hydrogenation reactions; copies of $^{31}P\{^{1}H\}$, ^{1}H, and $^{13}C\{^{1}H\}$ NMR spectra; and enantiomeric excess determination-and characterization details of hydrogenated products This material is available free of charge via the Internet at http://pubs.acs.org.

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Ir-PHOX-based phosphite-oxazoline catalysts, prepared in only 3 steps from available starting sources, have been successfully applied in the asymmetric hydrogenation of cyclic β-enamides providing better enantioselectivities than previous effective Ru- and Rh-catalysts (ee's up to 99%).