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Short communication

Chelate ring size effects of Ir(P,N,N) complexes: Chemoselectivity switch in the asymmetric hydrogenation of α,β-unsaturated ketones

Zsófia Császár[a], Eszter Z. Szabó[a], Attila C. Bényei[b], József Bakos[a], Gergely Farkas[a,*]

[a] Department of Organic Chemistry, University of Pannonia, Egyetem u. 10., H-8200 Veszprém, Hungary
[b] Department of Pharmaceutical Chemistry, University of Debrecen, Egyetem tér 1, H-4032 Debrecen, Hungary

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ABSTRACT

A novel, highly modular approach has been developed for the synthesis of new chiral P,N,N ligands with the general formula $Ph_2P(CH_3)CH(CH_2)_mCH(CH_3)NHCH_2CH_2(CH_2)_nN(CH_3)_2$ and $Ph_2P(CH_3)CHCH_2CH(CH_3)NHCH_2(CH_2)_n$-2-Py (*m*, *n* = 0, 1). The systematic variation of their P—N and N—N backbone led to the conclusion that the activity, chemo- and enantioselectivity in the hydrogenation of α,β-unsaturated ketones are highly dependent on the combination of the two bridge lengths. It has been found that a minor change in the ligand's structure, i. e. varying the value of *m* from 1 to 0, can switch the chemoselectivity of the reaction, from 80% C=O to 97% C=C selectivity.

1. Introduction

Transition metal catalyzed asymmetric hydrogenation of ketones is one of the simplest chemical transformations affording optically active secondary alcohols that serve as useful intermediates for the synthesis of biologically active compounds such as medicines, perfumes, and agrochemicals [1–4]. Since the development of highly efficient chiral ruthenium-diphosphine/diamine complexes by Noyori et al. for the asymmetric hydrogenation of ketones in the 1990s [5], the design and synthesis of novel and even more efficient transition metal catalysts still represents a challenging direction in this research area [6,7]. Besides ruthenium-based systems, chiral iridium-complexes proved to be highly active, selective and robust catalysts in the asymmetric hydrogenation of a broad range of ketonic substrates. In this contribution, Ir-complexes modified by potentially tridentate P,N,N ligands constitute a unique class of chiral catalysts due to their extremely high activity and selectivity, structural modularity and high substrate tolerance (Fig. 1). Recently, Zhou and coworkers developed spiro pyridine-aminophosphine (SpiroPAP) based Ir-catalysts that were utilized in the asymmetric hydrogenation of simple [8] and functionalized ketones (ketoesters [9–11], ketoacids [12], α-amino-ketones [13]) with outstanding activities (eg. TOF > 100,000 h^{-1} for acetophenone) and enantioselectivities (> 99% *ee*). To date the Ir-SpiroPAP system is the only Ir(P,N,N) catalyst used in the hydrogenation of α,β-unsaturated ketones toward enantioselective preparation of chiral 2-substituted acyclic allylic alcohols [14,15]. Zhang et al. synthesized Ir—P,N,N catalysts containing ferrocene based aminophosphine-oxazoline type chiral ligands (f-Amphox) and sucessfully used them in the enantioselective hydrogenation of simple ketones [16], α-hydroxy- [17] and halogenated ketones [18] and β-ketoesters [19] with remarkably high enantioselectivity and activity. Another ferrocene-containing ligand family has been developed by the workgroups of Hu and Zhang and applied in the Ir-catalyzed hydrogenation of aromatic ketones [20,21] and β-ketoesters [22] as well as for the hydrogenation of α-alkyl-β-ketoesters [23] via dynamic kinetic resolution. In addition to these systems Hu et al. reported on the synthesis of an oxazoline-containing tridentate ligand that exhibited good performance in the hydrogenation of β-ketoesters [24]. It should be pointed out that all of these ligands include aromatic moieties in the backbone which might decrease the conformational flexibility of the chelate ring. The Ir-complexes of these ligands are capable of producing chiral secondary alcohols with the same efficiency as the corresponding Ru-based systems, and in several cases even outperform their catalytic efficiency in terms of both activity and enantioselectivity.

A key factor in an efficient catalyst design is the careful stereoelectronic fine tuning of the ligands structure. In asymmetric transition metal catalysis, the majority of reports on ligand modifications have followed systematic variation of the simple spatial demands of the catalyst, and/or substituent controlled electronic tuning of the chiral ligands. Indeed, this trend can nicely be recognized regarding the above examples, as the structural modifications, marked with red color in Fig. 1, involve (i) the alteration of the phosphorus substituents (PAr_2), (ii) the modification of pendant side groups (R or X) or (iii) the variation of the relative configurations of the stereogenic elements.

* Corresponding author.
E-mail address: gerifarkas@almos.uni-pannon.hu (G. Farkas).

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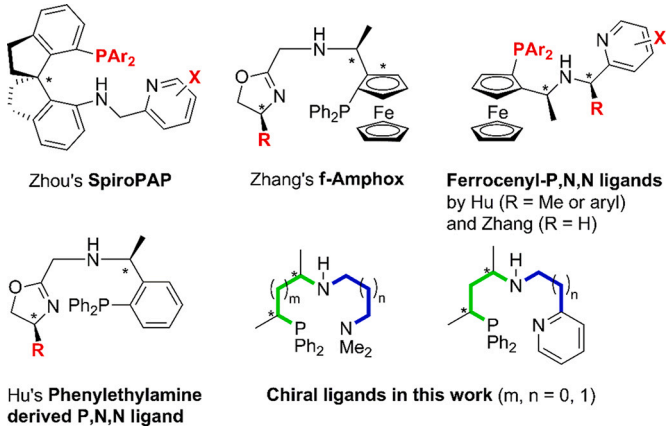


Fig. 1. Subclasses of chiral P,N,N ligands used in Ir-catalyzed asymmetric hydrogenation.

Generally, less common are instances of the manipulation of the chelate ring size, despite the fact that such changes can be, in many cases, readily implemented resulting in steric and also electronic alteration and producing similarly dramatic improvements in catalytic activity and enantioselectivity [25–27]. Surprisingly, the variation of the ring size of potentially tridentate ligands in catalysis is very rare [28–31] and to the best of our knowledge there is no such example concerning asymmetric catalytic transformations. However, as it was underlined by Crabtree and Peris, "this little studied area, analogous to bite angle effects in chelates, seems worth further efforts" [32].

In the present study we report on the development of a highly modular synthetic approach leading to a novel class of chiral P,N,N ligands based on two alkane-diyl backbones of different P,N and N,N tether lengths (Fig. 1). In order to compare the catalytic behavior of the new ligands, they were tested in the iridium catalyzed chemo- and enantioselective hydrogenation of enones, a challenging substrate class, with the intention to compare their activity, chemo- and enantioselectivity. Our primary aim was to vary the chelate ring size formed by the ligands and hence influence the bite angle and the conformational flexibility of the catalysts. Additionally, the effect of the reaction conditions and the substrate scope was carefully screened.

2. Results and discussion

2.1. Synthesis of the ligands

The novel ligands were synthesized in two simple steps. At first, enantiomerically pure (4*S*,5*S*)-4,5-dimethyl-1,3,2-dioxathiolane 2,2-dioxide (**1a**) or (4*R*,6*R*)- or (4*S*,6*S*)-4,6-dimethyl-1,3,2-dioxathiane-2,2-dioxide (**1b**) and the corresponding diamine were mixed in THF leading to aminoalkyl sulfates **2a-f** (Scheme 1). A remarkable feature of this methodology is that strong bases as deprotonating agents for the amines can be avoided. The addition of three equivalents of $LiPPh_2$ in THF provided the desired P,N,N (**L1-L6**) ligands in good yields. Both the ring opening reaction of the cyclic sulfate with the amine and the second substitution reaction take place with complete inversion at the stereogenic centers. The $^{31}P\{^1H\}$ NMR spectra of the compounds **L1-L6** exhibit one singlet line indicating the formation of one single diastereomer. It is important to note that the present synthetic methodology is of high modularity and does not require tedious multiple reactions steps. Concerning the structural versatility of the commercially available chiral (or non-chiral) cyclic sulfates and diamines the structural fine tuning of the corresponding ligands can easily be implemented without tedious workup procedures.

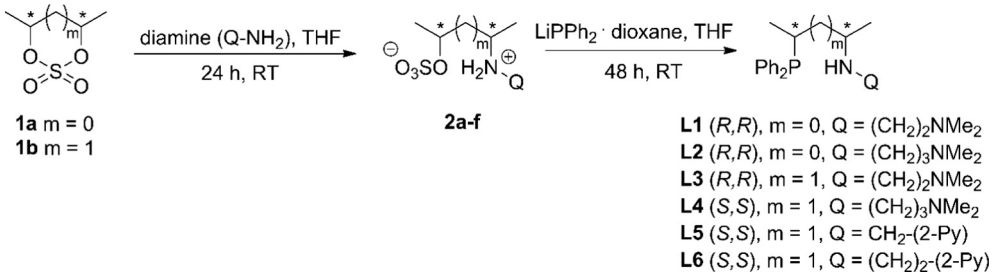
2.2. Catalytic studies

At first, we chose (*E*)-chalcone (**S1**) as a standard substrate for the Ir-catalyzed hydrogenation to screen ligands **L1-L6** (Scheme 2). Hydrogenation of **S1** in methanol in the presence of the Ir catalyst, synthesized in situ from $[Ir(COD)Cl]_2$ and chiral P,N,N ligand (P,N,N/Ir = 1), at a substrate catalyst molar ratio of 1000, 5 bar hydrogen pressure and room temperature afforded hydrogenation products **A1**, **B1** and **C1** in different ratio.

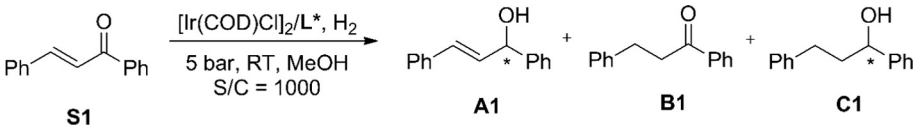
The reactions completed within 60 min with ligands **L2** and **L4** (Table 1, entries 2 and 4) and 87% conversion could be achieved with **L3** (entry 3). Catalysts with more rigid skeleton, i.e. ligands of shorter backbone(s) (**L1**) or pyridyl containing side chain (**L5** and **L6**), provided low turnovers. For the sake of comparison, we tested the bidentate analogue of ligand **L3**, with a simple N-ethyl substituent, under identical conditions in the hydrogenation reaction of **S1** (entry 7). No conversion could be achieved, indicating that the presence of the third coordination site is necessary to obtain catalytic turnover. Furthermore, it also suggests that the N atom of the side arm coordinates to the metal during the catalytic reaction forming an N,N chelate in addition to the P,N cycle. Zhou et al. reported that the introduction of a third coordination site to a P,N/Ir system (SpiroAP/Ir) lead to increased stability and activity (SpiroPAP/Ir) [8]. In this case the pronounced difference between the P,N and P,N,N systems was attributed to the ability of the former system to irreversibly form inactive dimers or trimers under hydrogenation conditions [33].

As the bidentate system was totally inactive in our case (entry 7), it was surmised that the introduction of the third coordination site not only prevents the formation of inactive metal species but through coordination to the metal may also change the conformation of the P,N chelate, thus potentially changing the substrate-catalyst interaction in the catalytic cycle. This is also in line with the data of Table 1, where the activity of the catalysts depends both on the structure of the P,N and the N,N backbone. The highest conversions could be achieved with ligands **L2** and **L4** (Table 1, entries 2 and 4) having the most flexible dimethylaminopropyl side chain.

The chemoselectivity of the reaction drastically changes with the length of the P,N backbone. Butane-2,3-diyl based systems **L1** and **L2** are less selective toward allylic alcohol **A1** (entries 1 and 2). In fact, **L2** provided saturated ketone **B1** with 94% chemoselectivity. Contrarily, ligands with pentane-2,4-diyl backbone and sp^3 N-atoms, **L3** and **L4**, proved to be rather selective to **A1**, giving 66 and 80% chemoselectivity, respectively (entries 3 and 4).



Scheme 1. Synthesis of chiral ligands **L1-L6**

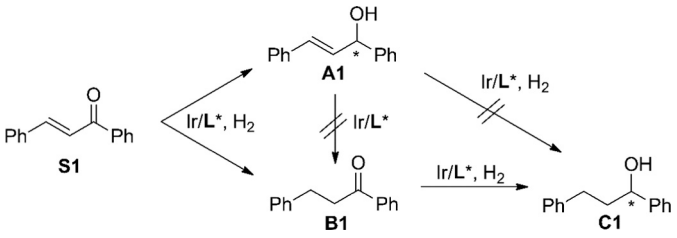


Scheme 2. Chemo- and enantioselective hydrogenation of (*E*)-chalcone (**S1**)

Ligands **L3** and **L4** were also highly enantioselective as the allylic alcohol **A1** was produced with 90 and 94% *ee*, respectively. Interestingly, increasing the length of the side chain, i.e. the ring size of the N,N-chelate, slightly increases the enantioselectivity. Ligands **L5** and **L6** with more rigid pyridyl-containing pendant side arm gave lower chemo- and enantioselectivities (entries 5 and 6).

In order to gain a deeper insight into the reaction pathways leading to the formation of **B1** and **C1**, racemic allylic alcohol **A1** as starting material was subjected to hydrogenation by using ligands **L2** and **L4** under identical conditions as in the first set of experiments (Table 1). No catalytic turnover could be achieved in either case. This experiment suggests that, in the catalytic reaction, product **B1** is formed by the direct hydrogenation of the C=C double bond of (*E*)-chalcone (**S1**) instead of the transition metal catalyzed isomerization [34] of the allylic alcohol **A1** (Scheme 3). The saturated alcohol **C1** is consequently a product of the C=O hydrogenation of **B1**. Consequently, the **L2**/Ir system having five-membered P,N chelate exhibits high C=C selectivity in the hydrogenation reaction, while the **L4**/Ir catalyst with six-membered P,N cycle switched chemoselectivity for the hydrogenation of C=O double bond. This phenomenon proves that the presence of the C=O double bond is a prerequisite for the hydrogenation of C=C moiety.

Encouraged by these observations, P,N,N ligands **L2** and **L4** were also utilized in the chemoselective hydrogenation of α,β-unsaturated carbonyl compounds **S2-S5** with distinct steric and **S6-S7** with different

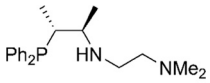
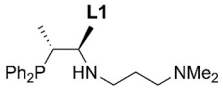
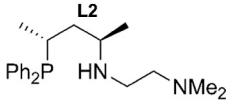
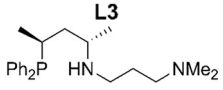
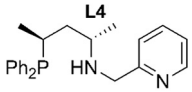
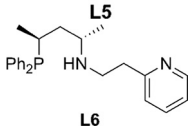
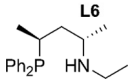


Scheme 3. Reaction pathways leading to the products of the enantioselective hydrogenation of **S1**

electronic properties. Based on the data of Table 2 it is clearly visible that the activity and selectivity of the two Ir–P,N,N systems are remarkably different with each conjugated substrates. This strongly suggest that the steric nature of the two systems are remarkably different. Albeit the electronic alteration of the substrate does not significantly change the activity and the chemoselectivity, the *ee* of hydrogenation of **S6**, containing electron withdrawing substituent, could be improved to 96%.

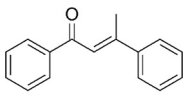
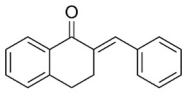
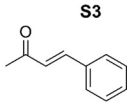
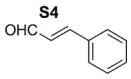
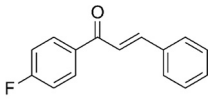
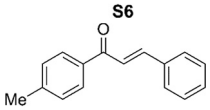
Although the exact explanation for the rather distinct catalytic performance of ligands **L1-L6** with different backbone length is currently unknown, several factors influencing activity and selectivity can be highlighted. The (i) *fac/mer* stereoselectivity in the coordination of the tridentate ligands [35], (ii) the hemilability of the terminal N-

Table 1
Ir-catalyzed chemo- and enantioselective hydrogenation of (*E*)-chalcone (**S1**): catalyst screening[a].

Entry	Ligand	Reaction time (h)	Conversion (%)[b]	A:B:C molar ratio (%)[b]	*Ee* of A (%)[c]
1		24 h	42	43:41:16	78
2	L1 	1 h	> 99 (91)[d]	2:94:4	–
3	L2 	1 h	87 (47)	66:15:19	90
4	L3 	1 h	> 99 (73)	80:8:12	94
5	L4 	1 h	20	72:23:5	78
6	L5 	1 h	10	34:60:4	64
7	L6 	24 h	0	–	–

[a] Reaction conditions: Catalyst: 12.12 μmol ligand and 5.06 μmol [Ir(*COD*)Cl]$_2$, substrate: 10 mmol (*E*)-chalcone, solvent: 6 ml MeOH, base: 100 μmol of *t*BuOK, H_2 pressure: 5 bar, temperature: RT.
[b] The conversion and chemoselectivity were determined by NMR spectroscopy. Values in brackets are isolated yields of **A1**.
[c] The enantioselectivity was determined by chiral HPLC.
[d] Isolated yield of product **B1**.

Table 2
Hydrogenation of α,β-unsaturated ketones **S2-S7** by using chiral P,N,N ligands **L2** and **L4**.[a]

Entry	Substrate	Ligand	P_{H2} (bar)	Conv. (%)[b]	Molar ratio of A in the product (%)[b]	*Ee* of A (%)[c]
1[d]	 **S2**	**L2**	5	> 99	> 99	86
2[d]		**L4**	5	23	> 99	70
3[e]	 **S3**	**L2**	15	98	85	76
4[e]		**L4**	15	6	–	–
5	 **S4**	**L2**	5	65	36	22
6		**L4**	5	> 99	97	36
7	 **S5**	**L2**	5	> 99	> 99	–
8		**L4**	5	> 99	> 99	–
9	 **S6**	**L2**	5	> 99	5	–
10		**L4**	5	> 99	81	96
11	 **S7**	**L2**	5	84	2	–
12		**L4**	5	95	77	92

[a] Reaction conditions: Catalyst: 12.12 μmol ligand and 5.06 μmol $[Ir(COD)Cl]_2$, substrate: 10 mmol, solvent: 6 ml MeOH, base: 100 μmol of *t*BuOK, reaction time: 1 h.
[b] The conversion and chemoselectivity were determined by NMR spectroscopy.
[c] The enantioselectivity was determined by chiral HPLC.
[d] Substrate: 2 mmol, reaction time: 24 h.
[e] Substrate: 2 mmol.

Table 3
Asymmetric hydrogenation of (*E*)-chalcone (**S1**)[a].

Entry	Solvent	Ligand	T (°C)	P_{H2} (bar)	Time (h)	Conv. (%)[b]	A:B:C molar ratio (%)[b]	*Ee* of A (%)[c]
1	MeOH/H_2O 85/15	**L2**	25	5	2	79	2:98:0	–
2		**L4**				90	67:18:15	88
3	MeOH/H_2O 70/30	**L2**	25	5	2	85	5:93:2	–
4		**L4**				91	63:22:15	88
5[d]	MeOH	**L2**	25	1	1	78	5:95:0	–
6[d]		**L4**				58	73:21:6	96
7	MeOH	**L2**	40	10	5 min	57	5:95:0	–
8		**L4**				> 99	74:8:18	94

[a] Reaction conditions: Catalyst: 12.12 μmol ligand and 5.06 μmol $[Ir(COD)Cl]_2$, substrate: 10 mmol, solvent: 6 ml MeOH, base: 100 μmol of *t*BuOK, reaction time: 1 h.
[b] The conversion and chemoselectivity were determined by NMR spectroscopy.
[c] The enantioselectivity was determined by chiral HPLC.
[d] Substrate: 2 mmol.

containing functionality capable of creating vacant coordination sites [32], (iii) the mutual interactions between the two (P,N and N,N) chelates affecting ring conformation and (iv) the magnitude of the bite angle in the catalytically active species may largely contribute to the diverse reactivity pattern. Nevertheless, the proper choice of the ligand backbone enabled the hydrogenation of α,β-unsaturated ketones carbonyl compounds with high activity, chemo- and enantioselectivity.

Finally, we compared the catalytic performance of the Ir-catalysts modified by **L2** and **L4** under different reaction conditions by varying the solvent, the pressure and the temperature (Table 3). The catalysts proved to be active and selective even in 70 *V*/*V*% aqueous methanol (MeOH/H_2O 70/30). At 1 bar hydrogen pressure the enantioselectivity of **A1** could be increased to 96% *ee*, while the chemoselectivity somewhat decreased. Interestingly, increasing the temperature to 40 °C the reaction was complete after 5 min and the *ee* remained unchanged compared to the experiment conducted at room temperature. This result corresponds to a TOF value of higher than 12,000 h^{-1}.

In conclusion, a novel highly modular synthetic approach has been developed for the synthesis of chiral tridentate P,N,N type ligands **L1-L6**. The new methodology enables the variation of the P,N and N,N bridge length as well as the stereoselective synthesis of the ligands in two simple steps. The novel compounds **L1-L6** were screened in the Ir-catalyzed chemo- and enantioselective hydrogenation of enones to investigate the effects of their backbone length on the activity and selectivity of the catalytic reactions. The rate and the selectivity of the asymmetric hydrogenation were strongly sensitive to the size of the formed chelate rings. By simply changing the size of the P,N chelate switched the chemoselectivity of the reaction. Furthermore, by properly

combining the backbone lengths high enantioselectivities (up to 96% *ee*) and chemoselectivities (98%) could be obtained. As a unique feature of the PNN/Ir systems, the hydrogenation reactions could also be performed in aqueous methanol solutions.

The substantial improvements of the chemo- and enantioselectivities and catalytic activities by the simple variation of the backbone length of P,N,N systems clearly indicate the high potential of this new strategy in successful catalyst design. We believe this can be applied to other catalytic reactions. A detailed mechanistic study of the ring size effects in the catalytic reaction is currently in progress in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.catcom.2020.106128.

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