Letter

Asymmetric hydrogenation of di-, tri- and tetrasubstituted minimally functionalized olefins and cyclic #-enamides with easily accessible Ir-P,oxazoline catalysts

Maria Biosca, Marc Magre, Oscar Pàmies, and Montserrat Diéguez

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Asymmetric hydrogenation of di-, tri- and tetrasubstituted minimally functionalized olefins and cyclic β-enamides with easily accessible Ir-P,oxazoline catalysts.

Maria Biosca, Marc Magre, Oscar Pàmies* and Montserrat Diéguez*

Universitat Rovira i Virgili. Departament de Química Física i Inorgànica. C/ Marcel·lí Domingo 1, 43007 Tarragona, Spain.

ABSTRACT: We have developed a family of Ir-P,oxazoline catalysts for asymmetric hydrogenation. These catalysts, with a simple modular architecture, have shown a high tolerance to the olefin geometry and substitution pattern, and to the presence of several neighboring polar groups. Thus, they were able to successfully hydrogenate di-, tri- and tetrasubstituted minimally functionalized olefins (*ee*'s up to 99%). The excellent catalytic performance was also extended to the hydrogenation of cyclic β-enamides.

KEYWORDS: Iridium, P,N-ligands, asymmetric hydrogenation, unfunctionalized olefins, cyclic β-enamides.

Asymmetric hydrogenation (AH) of olefins is a well-known approach to introduce chirality into target molecules. It has perfect atom economy, uses low catalyst loading and it is operationally simple.[1] The AH of functionalized olefins has been thoroughly studied for decades and can now be considered a mature field.[2] Rh- and Ru-catalysts, mostly based on diphosphine ligands have performed the best. Their performance is critically influenced by the substrate coordinative groups that guide the chiral transfer to the product. When those coordinative groups are absent (minimally functionalized olefins), the introduction of chirality becomes a much greater challenge and, in this field, Ir-catalysts have performed the best.[3] The best catalysts have two characteristics in common: (i) they contain P,N ligands and (ii) their optimal structure is highly dependent on the geometry and substitution pattern of the olefin.[3] The consequence is that for each particular olefin type a different ligand family needs to be developed. Figure 1 shows a selection of the most efficient chiral ligands and illustrates how different the ligand motifs need to be to achieve high enantioselectivity for each particular olefin substitution pattern. It is also important to notice that different degrees of catalyst development have been achieved for each olefin substitution pattern.[3] The most successful cases have been reported for trisubstituted olefines[3] and, to a less extend, for disubstituted[4]. The AH of tetrasubstituted unfunctionalized substrates is still underdeveloped. Only four publications have reported high catalytic performance for certain substrates,[5] being the Pfaltz catalysts the ones that work under milder conditions and are applicable to more substrates. The discovery of a family of catalysts with a wide substrate scope remains a central task in AH of unfunctionalized olefins. A desired additional condition is that the catalyst family should be synthesized from available starting materials and be easy to handle.

Here we report the first P,N-ligand family (**L1**-**L6**, Scheme 1) that performs well for the Ir-catalyzed AH of different types of unfunctionalized olefins. From a common skeleton, the right choice of either a phosphite group or phophinite group results in ligands that are suitable for di-, tri- and tetrasubstituted unfunctionalized olefins. The "ligand family" concept helps to reduce the time dedicated to ligand design and preparation and facilitates the discovery of the optimal ligand for a wide range of substrates. This family has also been successfully applied to the AH of challenging functionalized cyclic β-enamides.[6]

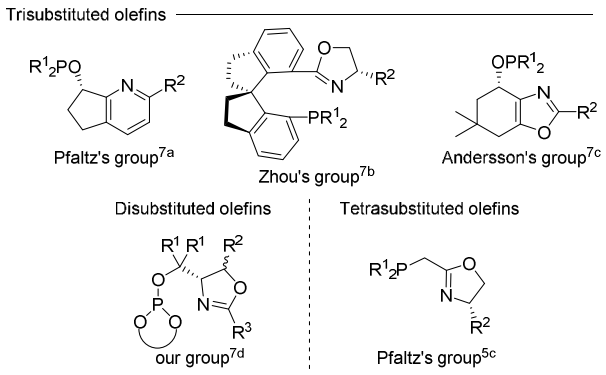
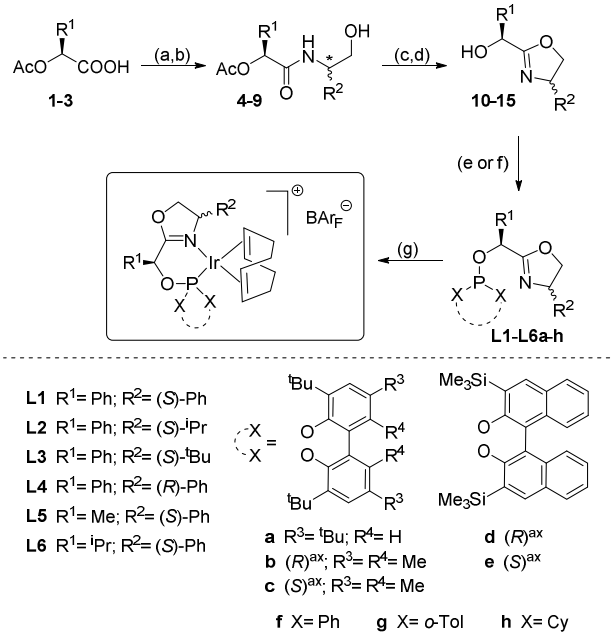


Figure 1. Representative ligands developed for the Ir-catalyzed AH of di-, tri- and tetrasubstituted minimally functionalized olefins.[5c,7]

The new Ir-catalyst precursors [Ir(cod)(**L1**-**L6a**-**h**)]BAr_F, with the P,oxazoline ligands were prepared in few steps from readily available α-acetoxy acids **1**-**3** (Scheme 1).[8] From a common skeleton, several ligand modules can be independently varied to form the family of catalysts. The variations include: the substituents and configurations at the ligand backbone (R^1); the substituents and configura-

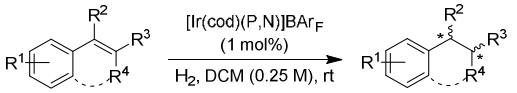
tions at the oxazoline (R^2); the substituents and configuration of the biaryl phosphite moiety (**a**-**e**); and the type of P-donor group (phosphite or phosphinite). Compounds **1**-**3**, already incorporate the desired diversity in the substituents at the alkyl backbone chain (R^1). Compounds **1**-**3** were first coupled with the desired chiral amino alcohol to afford amides **4**-**9**. This step introduced diversity in the substituents and configuration of the oxazoline moiety (R^2). Compounds **4**-**9** were then converted to the hydroxyl-oxazolines **10**-**15** by reaction with diethylaminosulfur trifluoride (DAST) followed by standard acetate deprotection. Reaction of the hydroxyl-oxazolines with the corresponding phosphorochloridite afforded the phosphite-oxazoline ligands (**L1**-**L6a**-**e**); the reaction with the chlorophosphine afforded the phosphinite-oxazoline ligands (**L1**-**L6f**-**h**). Ligand coordination by reaction with 0.5 equiv of $[Ir(\mu\text{-Cl})(cod)]_2$ followed by in situ Cl^-/BAr_F^- counterion exchange led to the desired catalyst precursors $[Ir(cod)(\mathbf{L1}\text{-}\mathbf{L6a}\text{-}\mathbf{h})]BAr_F$ as orange air stable solids.

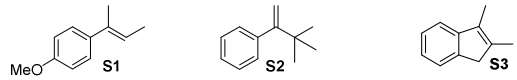


Scheme 1. Synthesis of $[Ir(cod)(\mathbf{L1}\text{-}\mathbf{L6a}\text{-}\mathbf{h})]BAr_F$ catalyst precursors. (a) $SOCl_2$, DCM, reflux, 3 h; (b) aminoalcohol, NEt_3, DCM, rt, 5 h; (c) DAST, K_2CO_3, DCM, -78 °C to rt for 3 h; (d) NaOH (aq), EtOH, 0 ºC, 3 h; (e) $ClP(OR)_2$, Py, toluene, -78 °C to rt, 16 h; (f) $ClPR_2$, NEt_3, DMAP, toluene, rt, 20 min; (g) $[Ir(\mu\text{-Cl})(cod)]_2$, DCM, reflux, 1 h then $NaBAr_F$, H_2O, rt, 30 min.

$[Ir(cod)(\mathbf{L1}\text{-}\mathbf{L6a}\text{-}\mathbf{h})]BAr_F$ complexes were first evaluated in the hydrogenation of model di-, tri- and tetrasubstituted minimally functionalized alkenes (**S1**-**S3**; Table 1). For comparison, catalyst precursors were tested in the optimal reaction conditions reported in previous studies with other P,N-ligands.[3] High enantioselectivities, comparable to the best ones reported,[3] were obtained for all substrates, regardless of the olefin substitution pattern.

Table 1. Ir-catalyzed AH of model tri-, di- and tetrasubstituted minimally functionalized olefins **S1**–**S3**.[a]





P,N	%Conv[b]	% ee[c]	%Conv[b]	% ee[c]	%Conv[b]	% ee[c]
	S1		**S2**		**S3**	
L1a	100	58 (*R*)	100	96 (*S*)	39[d]	37 (*S*,*S*)
L1b	100	75 (*R*)	100	88 (*S*)	14[d]	29 (*S*,*S*)
L1c	100	67 (*S*)	100	40 (*S*)	25[d]	16 (*S*,*S*)
L1d	100	92 (*R*)	100	93 (*S*)	22[d]	23 (*S*,*S*)
L1e	100	68 (*S*)	100	42 (*S*)	36[d]	18 (*S*,*S*)
L1f	100	60 (*R*)	100	81 (*S*)	100	84 (*S*,*S*)
L1g	100	70 (*R*)	100	82 (*S*)	100	80 (*S*,*S*)
L2a	100	30 (*R*)	100	95 (*S*)	25[d]	82 (*S*,*S*)
L2b	100	64 (*R*)	100	89 (*S*)	10[d]	50 (*S*,*S*)
L2f	100	38 (*R*)	100	80 (*S*)	100[e]	97 (*S*,*S*)
L2g	100	44 (*R*)	100	84 (*S*)	100	87 (*S*,*S*)
L2h	100	15 (*R*)	100	54 (*S*)	100	75 (*S*,*S*)
L3a	100	9 (*R*)	100	97 (*S*)	5[d]	34 (*R*,*R*)
L3b	100	88 (*R*)	100	77 (*S*)	<5	nd[f]
L4a	100	76 (*S*)	100	98 (*R*)	50[d]	64 (*S*,*S*)
L4d	100	0	100	74 (*R*)	5[d]	4 (*S*,*S*)
L4e	100	93 (*S*)	100	92 (*R*)	24	47 (*R*,*R*)
L4f	100	71 (*S*)	100	85 (*R*)	100	75 (*R*,*R*)
L4g	100	66 (*S*)	100	83 (*R*)	100	70 (*R*,*R*)
L4h	100	80 (*S*)	100	85 (*R*)	100	20 (*R*,*R*)
L5a	100	78 (*R*)	100	92 (*S*)	15[d]	42 (*S*,*S*)
L5d	100	98 (*R*)	100	92 (*S*)	10[d]	25 (*S*,*S*)
L5e	100	40 (*S*)	100	10 (*S*)	15[d]	21 (*S*,*S*)
L6a	100	81 (*R*)	100	96 (*S*)	20[d]	53 (*S*,*S*)
L6d	100	94 (*R*)	100	91 (*S*)	13[d]	12 (*S*,*S*)
L6e	100	30 (*R*)	100	60 (*S*)	25[d]	30 (*S*,*S*)

[a] Reaction conditions: 1 mol% Ir-catalyst precursor, substrate (0.5 mmol), DCM, rt for 4 h, P_{H_2} = 50 bar (for **S1** and **S3**), 1 bar (for **S2**). [b] Conversions determined by GC. [c] Enantiomeric excesses determined by chiral GC. [d] Reactions carried out for 20 h. [e] Reaction performed at 25 bar H_2. [f] not determined.

The results also reveal several trends in the obtained enantioselectivities: (i) the highest enantioselectivity in the reduction of di- and trisubstituted olefins (ee's up to 98%,) were obtained with phosphite-based ligands (eg. **L4a** and **L5d**) while phosphinite-based ligands were required for tetrasubstituted olefins (cf. **L2f** vs. **L2a**, ee's up to 97%),[9] (ii) oxazolines derived from expensive *tert*-leucinol (eg. ligands **L3**) were not needed to achieve high ees, which is an important advantage over the most wide-

ly used P-oxazoline ligands (e.g. PHOX-derived ligands);[3] (iii) finally, for substrates **S1** and **S2**, both enantiomers of the hydrogenated products were accessible in high enantioselectivities by using diastereoisomeric ligands (e.g. 98% (*R*) for **S1** with **L4a** vs 96% (*S*) with **L1a**; or 93% (*S*) for **S2** with **L4a** vs 98 (*R*) with **L5d**).

We then performed a broad unfunctionalized substrate screening that included di-, tri- and tetrasubstituted olefins, different geometries (*E* and *Z*), and different neighboring polar groups. A summary of the AH results of 53 olefins is shown in Figure 2 (see S.I. for a complete series of results). As seen previously, the best results for di- and trisubstituted olefins were achieved with phosphite-based ligands and for tetrasubstituted with phosphinite-based ligands. The other ligand parameters had a different influence depending on the substrate and had to be specifically selected to obtain high enantioselectivities.

For the reduction of minimally unfunctionalized trisubstituted olefins, the new catalyst precursors were found to be well suited for those with *E*-geometry (**S4**-**S5**) and for those with the challenging *Z*-geometry (**S6**) and the exocyclic olefin (**S7**), obtaining in all cases both enantiomers of the reduced products. They also worked well for olefins with a variety of relevant neighboring polar groups such as α,β-unsaturated esters, ketones and lactames, vinyl boronates and enol phosphinates (**S8**-**S32**). All the substrates were hydrogenated with excellent enantiocontrol (*ee*'s up to >99%), comparable to the best ones reported.[3] In addition, for each type of neighboring group, the enantioselectivities were quite independent on the electronic and steric nature of the substituents decorating such motifs. The effective hydrogenation of such a range of olefins is of great importance since their reduced products are key structural chiral units found in many high value chemicals (e.g. α- and β-chiral ketones and carboxylic acid derivatives are ubiquitous in natural products, fragrances, agrochemicals, and drugs).[10]

Our catalyst precursors also proved to be highly competent in the hydrogenation of a broad range of disubstituted olefins (**S33**-**S45**). Excellent enantioselectivities were achieved (up to >99% *ee*) in the AH of a series of 1,1-disubstituted (hetero)aryl/alkyl olefins and also aryl- and alkyl-enol phosphinates. The reduction α-alkylstyrenes with less sterically demanding alkyl substituents proceeded with somewhat lower enantioselectivies (see S.I, for details), like in previous successful reports.[4,11]

Finally, for tetrasubstituted olefins our catalyst precursors proved to be highly efficient in the reduction of several indenes (**S46**-**S50**) with different substituents at both the benzylic and vinylic position as well as substituents in the aryl ring (*ee*'s up to 98%), under the comparable mild reactions conditions developed by Pfaltz.[5c] This improved previously reported results. The high enantiocontrol for the more challenging 3,4-dimehtyl-1,2-dihydronapthalene and the acyclic tetrasubstituted olefins (**S51**-**S56**; *ee*'s up to 98%), is even more remarkable, surpassing the best results reported so far. For acyclic substrates, only the Pfaltz's catalysts have been successful but enantioselectivity was high (97% *ee*) in the AH of one substrate only. Interestingly the hydrogenation of the latter substrates can be achieved at only 1 bar of H_2. It should be noted that the more rigid the tretrasubstituted olefin is, the less bulky phosphinite moieties are required to reach the maximum enantioselectivity. For the more rigid cyclic indene derivatives **S3** and **S45**-**S50**, the best catalytic performance is reached with the phosphinite-based ligand **L2f**, while for the less rigid cyclic substrate **S51**, the phosphinite ligand **L2g**, with a more bulky tolyl group is needed. Finally, the even less rigid acyclic substrates (**S52**-**S56**) require the diastereoisomeric ligand **L4h**, which has the bulkiest cyclohexenyl phosphinite group.

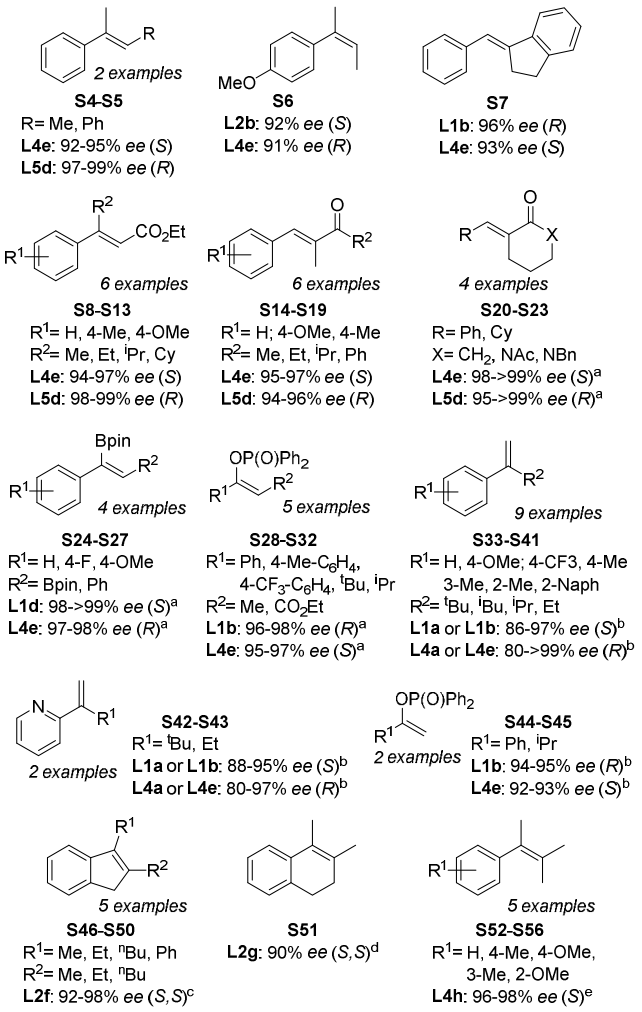


Figure 2. Selected results for AH of a range of di-, tri- and tetrasubstituted minimally functionalized olefins. Typical reaction conditions: 1 mol% of [Ir(cod)(P-N)]BAr_F, 50 bar H_2, DCM, rt for 4 h. Full conversions were achieved in all cases. [a] Reactions carried out at 50 bar H_2 for 24 h. [b] Reactions carried out at 1 bar H_2 for 4 h. [c] Reactions carried out at 25 bar H_2 for 24 h. [d] Reaction carried out at 75 bar H_2 for 24 h. [e] Reactions carried out at 1 bar H_2 for 24 h.

Encouraged by these remarkable results, we decided to study the AH of cyclic β-enamides (Figure 3) which are a challenging type of functionalized olefins.[6] While the

reduction of α-enamides can be carried out with good success,[2] the AH of β-enamides remains one of the puzzling transformations, albeit the corresponding products are key units in many drugs and biologically active natural products such as Rotigotine,[12a] Alnespirone[12b] and Robalzotan[12c]. We found that catalyst precursors with ligands **L4e** and **L5d** provided both enantiomers of the hydrogenated products in high enantioselectivities (*ee*'s up to 99%) for a range of cyclic β-enamides, including the less studied enamides derived from 3-chromanones. These results are comparable to the best one reported in the literature.[6]

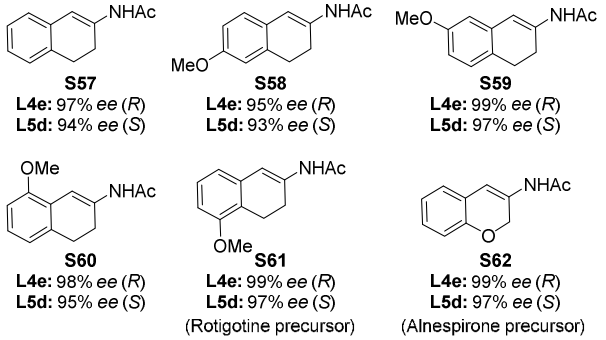


Figure 3. Selected hydrogenation results for the AH of cyclic β-enamides. Typical reaction conditions: 1 mol% of [Ir(cod)(P-N)]BAr_F, 50 bar H_2, DCM, rt for 24 h. Full conversions were achieved in all cases.

In summary, we have presented the first Ir-P,oxazoline catalytic family, with a simple modular architecture, that is able to successfully hydrogenate di-, tri- and tetrasubstituted minimally functionalized olefins (*ee*'s up to 99%). This family of catalysts has been synthesized in a few steps from unexpensive starting materials and are solid and stable in air. From a common skeleton, the right choice of either a phosphite group or phophinite group gives ligands that are suitable for di-, tri- and also tetrasubstituted olefins (62 examples). Improving previous results reported, these catalysts are able to efficiently reduce a range of indenes and the challenging 1,2-dihydro-napthalene (ee's up to 98%) and also a range of the most elusive acyclic olefins with unprecedented enantioselectivities (ee's up to 98%) under mild reaction conditions. The catalysts not only exhibited an unprecedented high tolerance to the geometry and steric constrains of the olefin, but they also could tolerate different functional groups very well. Thus, a broad range of olefins containing both minimally coordinative groups (e.g. α,β-unsaturated carboxylic esters, enones, lactames, vinyl boronates and enol phosphinates) and coordinative groups (the challenging β-enamides) could be hydrogenated with high levels of enantioselectivity.

ASSOCIATED CONTENT

AUTHOR INFORMATION

Corresponding Author

* E-mail for O.P.: oscar.pamies@urv.cat
* E-mail for M.D.: montserrat.dieguez@urv.cat

Notes

The authors declare no competing financial interest.

Supporting Information. Preparation, characterization details and copies of NMR spectra of [[Ir(cod)(**L1-L6a-h**)]BAr_F complexes. General procedure for the asymmetric hydrogenation. Characterization details and methods for enantiomeric excess determination of hydrogenated products. Complete series of results for the asymmetric hydrogenation of unfunctionalized olefins **S4-S56** and cyclic β-enamide **S57**. Copies of NMR and GC/HPLC traces for all hydrogenated products. Deuterium labelling experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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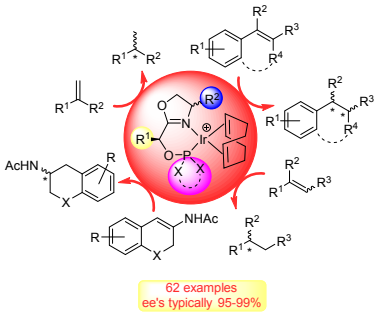
62 examples
ee's typically 95-99%