Asymmetric Hydrogenation

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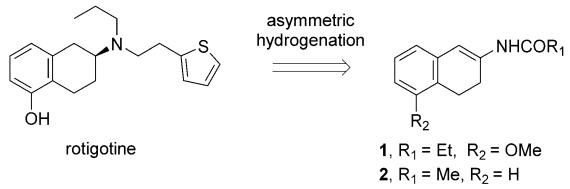
Highly Enantioselective Iridium-Catalyzed Hydrogenation of Cyclic Enamides

Ernest Salomó, Sílvia Orgué, Antoni Riera, and Xavier Verdaguer**

Dedicated to Professor Miquel A. Pericàs on the occasion of his 65th birthday

Abstract: *The MaxPHOX–Ir catalyst system provided the highest selectivity ever reported for the reduction of cyclic enamides derived from α- and β-tetralones. This result indicates that iridium catalysts are also proficient in reducing alkenes bearing metal-coordinating groups. In the present system, selectivity was pressure-dependent: In most cases, a decrease in the H_2 pressure to 3 bar resulted in an increase in enantioselectivity. Moreover, the process can be carried out in environmentally friendly solvents, such as methanol and ethyl acetate, with no loss of selectivity.*

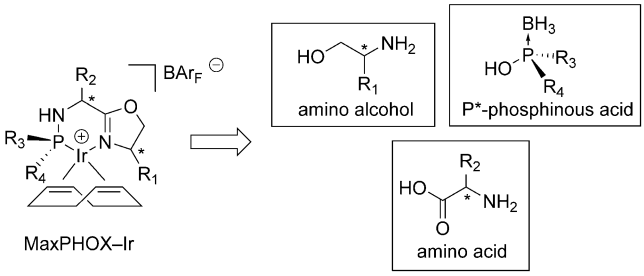


Scheme 1. Asymmetric hydrogenation as a route to rotigotine, a dopamine agonist for the treatment of Parkinson's disease.

Since its advent, metal-catalyzed asymmetric hydrogenation has attracted considerable interest from academia and industry,[1] because it is one of the best methods to introduce chirality into molecules. Numerous efficient catalytic systems based on Ru, Rh, and Ir are now available that provide near total selectivity in the hydrogenation of various prochiral alkenes.[2] However, for some substrates, attaining high selectivity remains a challenge. Such substrates include cyclic enamides derived from α- and β-tetralones. The asymmetric hydrogenation of these substrates is highly desirable, since the derived chiral amines have key therapeutic properties.[3] For example, rotigotine, a dopamine agonist used for the treatment of Parkinson's disease, can be prepared in enantiomerically enriched form through hydrogenation of the corresponding 3,4-dihydronaphthalene precursor **1** (Scheme 1).[4]

Until now, the asymmetric hydrogenation of cyclic enamides has relied on the use of chiral Rh and Ru catalysts. However, complete control of the stereoselectivity of this process has remained elusive. With Ru–binap systems, Bruneau and co-workers and Ratovelomanana-Vidal and co-workers reported up to 90–95% *ee* in the reduction of the parent compound *N*-(3,4-dihydronaphthalen-2-yl)acetamide (**2**).[5] Similar results have been obtained with Rh catalysts. Pizzano and co-workers reported 93% *ee* with a phosphine–phosphinite ligand.[6] Reek and co-workers observed the formation of the product with 94% *ee* in the hydrogenation of **2** with a supramolecular Rh catalyst.[7] Recently, Tang and co-workers reported the reduction of **2** in the presence of a Rh catalyst with a deep chiral pocket to give the product with 96% *ee*.[8]

We recently developed a novel route to bulky P-stereogenic phosphine ligands through S_N2@P reactions.[9] We envisioned that this methodology could provide access to a library of phosphine–oxazoline ligands with the general structure depicted in Scheme 2. A key feature of this ligand system (MaxPHOX) is that it contains three stereogenic centers that can be introduced from three separate and simple building blocks. We considered that the structural diversity arising from the different possible configurations and substitution patterns would make MaxPHOX a powerful ligand template for catalysis. To test this hypothesis, we undertook



Scheme 2. The P-stereogenic MaxPHOX ligands can be assembled from simple and independent building blocks. BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

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the synthesis of a small library of MaxPHOX–Ir catalysts and examined their performance in the asymmetric hydrogenation of cyclic enamides.

Chiral iridium–N,P complexes have been developed into the catalysts of choice for the hydrogenation of nonfunctionalized and minimally functionalized alkenes.[10] However, little attention has been paid to the use of such catalytic systems for the hydrogenation of alkenes bearing a metal-coordinating group.[11]

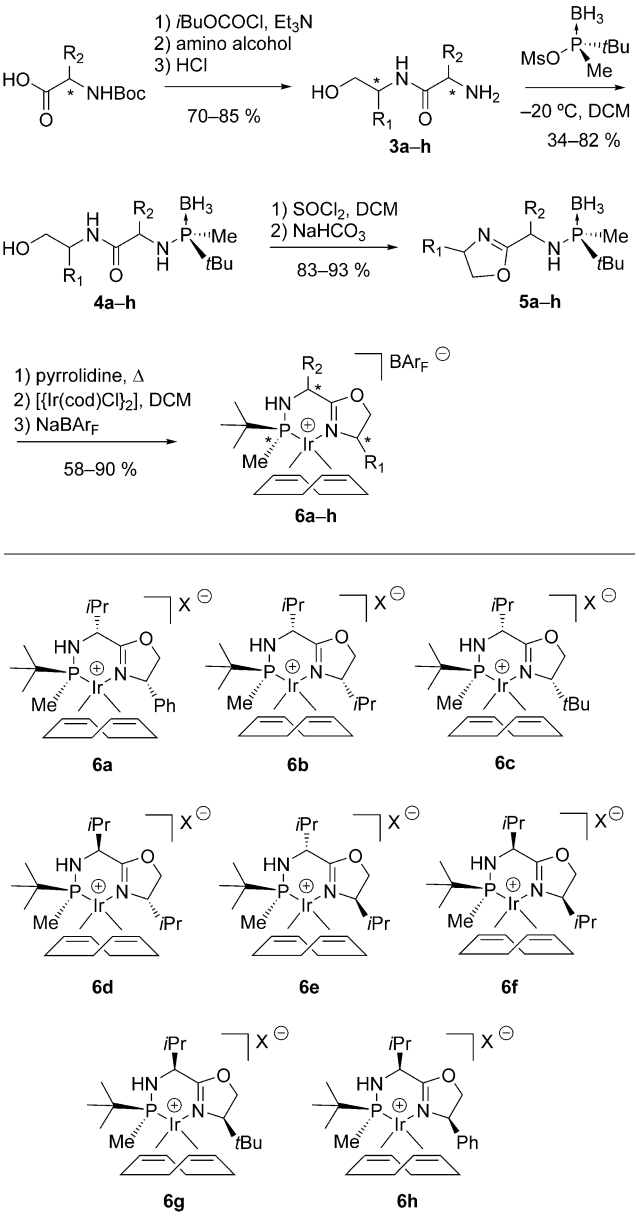
Herein we report the synthesis of a MaxPHOX–Ir catalyst library. This library enabled us to identify the structural features necessary for complete control of enantioselectivity in the hydrogenation of enamides derived from β-tetralones. Thus, we show how iridium-based catalysts outperform the best Ru and Rh systems for the hydrogenation of this class of alkenes.

The optimized synthesis of the MaxPHOX catalyst library is shown in Scheme 3. The N-Boc-protected amino acid was coupled to the corresponding amino alcohol by the use of isobutyl chloroformate. Removal of the Boc group afforded the corresponding amino alcohols **3a–h**, which were subsequently coupled to the chiral phosphinyl mesyl anhydride derived from (*S*)-*tert*-butyl(methyl)phosphinous acid borane[9,12,13] with inversion of configuration at the P center to provide the open-chain borane-protected aminophosphine alcohols **4a–h**. This key coupling reaction in the synthetic sequence is highly chemoselective for amine nucleophiles; no reaction was observed at the alcohol position. Next, **4a–h** were subjected to alcohol activation and base-induced chain cyclization to produce the corresponding borane-protected phosphine–oxazoline ligands **5a–h**. We found that the ligand synthesis was more general and efficient when the oxazoline cyclization was carried out at a later stage. Finally, removal of the borane protecting group with neat pyrrolidine, treatment with $[\{Ir(cod)Cl\}_2]$, and counterion exchange with $NaBAr_F$ afforded the corresponding MaxPHOX–Ir complexes **6a–h** in good to excellent yields.

Complexes **6a–h** had the same *S* configuration at the P center.[12] The four possible diastereomers with isopropyl groups at the tail and the oxazoline positions were synthesized ((*S*$_P$,*R*,*S*)-**6b**, (*S*$_P$,*S*,*S*)-**6d**, (*S*$_P$,*R*,*R*)-**6e**, (*S*$_P$,*S*,*R*)-**6f**). We also synthesized complexes **6a**, **6c**, **6g**, and **6h** to study the effect of the substituent on the oxazoline heterocycle.

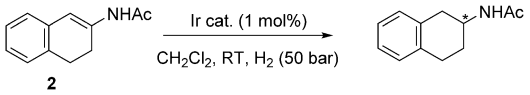
We then studied the hydrogenation of *N*-(3,4-dihydronaphthalen-2-yl)acetamide (**2**) with this small library of catalysts (Table 1). When the hydrogenation reaction was carried out at a catalyst loading of 1 mol% under 50 bar of H_2 in CH_2Cl_2 at room temperature with catalysts bearing the same substituents but with different relative configurations (**6b**, **6d**, **6e**, **6f**), matched–mismatched behavior with respect to the configurations at the oxazoline and P center became clear. With catalysts **6e** (***S***$_P$,*R*,***R***) and **6f** (***S***$_P$,*S*,***R***) with the matched configuration, the selectivity increased to 96 and 97% *ee*. Finally, when we changed the substituent on the oxazoline ring to a *tert*-butyl group and kept the best relative configuration found (***S***$_P$,*S*,***R***; catalyst **6g**), we obtained the product of the hydrogenation of **2** with over 99% *ee*.

With the second-best catalyst **6f**, we next studied the effect of the solvent and hydrogen pressure on the hydrogenation of cyclic enamides. When DCM was used as the solvent, a decrease in hydrogen pressure resulted in an increase in selectivity (Table 2, entries 1–3). Reactions at 10 and 3 bar of hydrogen resulted in complete conversion and total enantioselectivity (99% *ee*). Environmentally friendly solvents, such as methanol and ethyl acetate, also proved appropriate for the present catalytic system (Table 2, entries 4–8). A similar dependence of selectivity on the hydrogen pressure was found for these solvents. At 10 bar of hydrogen, 99% *ee* was reached in MeOH (Table 2, entry 5). Also in EtOAc, the pressure could be lowered to 3 bar to enable total conversion and selectivity (Table 2, entry 8). Therefore, a catalyst with a *tert*-butyl-substituted oxazoline group is not mandatory for complete stereocontrol



Scheme 3. Synthesis of MaxPHOX ligands and the corresponding iridium complexes. cod = 1,5-cyclooctadiene, DCM = dichloromethane, Ms = methanesulfonyl.

Table 1: Hydrogenation of *N*-(3,4-dihydronaphthalen-2-yl)acetamide. Influence of the oxazoline substituent and the relative configuration of the catalyst on the selectivity.[a]

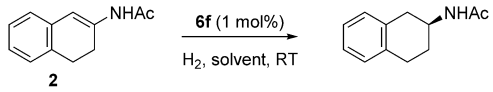


R_1	Relative configuration of the catalyst			
	S_PRS	S_PSS	S_PRR	S_PSR
Ph	58% ee **6a**			94% ee **6h**
i-Pr	3% ee **6b**	77% ee **6d**	96% ee **6e**	97% ee **6f**
t-Bu	75% ee **6c**			>99% ee **6g**

R	*S*	*ee* (%)
		0-25
		25-50
		50-75
		75-100

[a] Complete conversion was observed in all cases, as determined by ^{1}H NMR analysis of the crude reaction mixtures after 24 h at room temperature; *ee* values were determined by HPLC analysis on a chiral stationary phase.

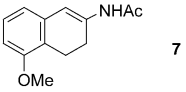
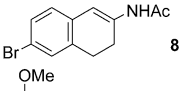
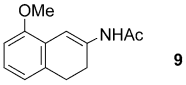
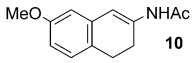
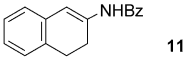
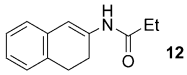
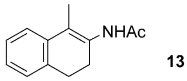
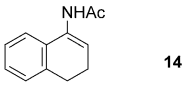
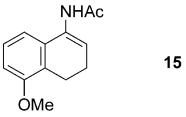
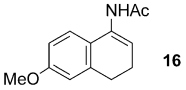
Table 2: Effect of the solvent and H_2 pressure.



Entry	Solvent	H_2 pressure [bar]	Conversion [%][a]	*ee* [%][b]
1	DCM	50	100	97
2	DCM	10	100	99
3	DCM	3	100	99
4	MeOH	50	100	96
5	MeOH	10	100	99
6	EtOAc	50	100	95
7	EtOAc	10	100	96
8	EtOAc	3	100	99

[a] Conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] The *ee* value was determined by HPLC analysis on a chiral stationary phase.

Table 3: Hydrogenation of cyclic enamides with MaxPHOX–Ir catalysts.[a]

Entry	Substrate	Catalyst	H_2 [bar]	Solvent	*ee* [%]
1	 **7**	**6g**	50	DCM	99
		6f	3	EtOAc	99
2	 **8**	**6g**	50	DCM	99
		6f	3	EtOAc	99
3	 **9**	**6f**	3	EtOAc	99
4	 **10**	**6f**	3	EtOAc	99
5	 **11**	**6f**	3	DCM	99
6	 **12**	**6g**	3	DCM	99
7	 **13**	**6g**	50	DCM	82
			3	DCM	99
8	 **14**	**6f**	3	DCM	99
9	 **15**	**6g**	3	DCM	99
10	 **16**	**6g**	3	DCM	99

[a] All reactions were conducted with a 1 mol% catalyst loading. Full conversion was observed at room temperature (24 h), as determined by ^{1}H NMR spectroscopy.

of the hydrogenation. Complete selectivity was also observed when the hydrogen pressure was lowered to 3–10 bar and the most cost-effective catalyst **6f** ($R_1 = i$Pr) was used.

Once the structural features of the catalyst and the reactions conditions had been optimized, we hydrogenated various other cyclic enamides to demonstrate the scope of the present catalytic system (Table 3). The hydrogenation of acetyl enamides derived from β-tetralone with various substitution patterns of the fused benzene ring occurred with complete selectivity with the catalyst **6f** ($R_1 = i$Pr) in ethyl acetate under 3 bar of hydrogen (Table 3, entries 1–4). Notably, substrate **7** is a precursor of rotigotine (Table 3, entry 1). Changes in the amido group on the enamide had no effect on the selectivity. Thus, the benzoyl and propanoyl enamides **11** and **12** were also reduced to the desired product with 99% *ee* in DCM at low H_2 pressure (Table 3, entries 5 and 6). Most notably, the reduction of the tetrasubstituted enamide **13** also occurred with high selectivity. Whereas reduction at 50 bar provided the product with only 82% *ee*, when the hydrogen pressure was lowered to 3 bar, the reduction product was again obtained with 99% *ee* (Table 3, entry 7). Finally, we addressed the reduction of acetyl enamides derived from α-tetralone, which are known to be difficult substrates for asymmetric hydrogenation.[14] Thus, with catalyst **6f**, the parent substrate **14** was reduced at room temperature to the desired product with 99% *ee* (Table 3, entry 8). In a similar manner, the products of the reduction of methoxy-substituted acetamides **15** and **16** were obtained with 99% *ee* (Table 3, entries 9 and 10).

The X-ray crystal structure of the most efficient catalyst **6g** (enantiomer) is depicted in Figure 1.[15] The six-membered metallacycle adopts a boatlike conformation. Interestingly, the bulky *tert*-butyl groups on the oxazoline ring and phosphorous atom are *syn* to each other on the same face of the metallacycle. The catalytic activity observed in coordinating solvents, such as EtOAc and MeOH, suggests the substrate binds in a bidentate manner to the cationic Ir complex.[16] Although the solid-state conformation of precatalyst **6g** might not be the active conformation in solution, it is reasonable to assume that the directing amide group binds to an axial position away from the bulky *tert*-butyl groups, whereas the alkene binds equatorially *trans* to phosphorus.[17] It was recently demonstrated that iridium(III) dihydride

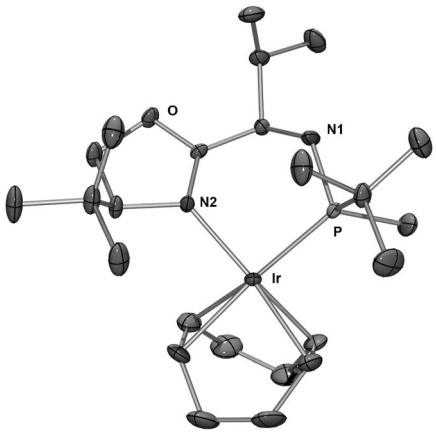


Figure 1. X-ray crystal structure of complex **6g** (enantiomer). ORTEP drawing with ellipsoids shown at 50% probability. The BAr_F counterion and a solvent molecule have been omitted for clarity.

alkene complexes rapidly isomerize, and that a minor iridium–alkene isomer can lead to the major hydrogenation product.[18] The dependence of the selectivity on the hydrogen pressure suggests that hydrogen is involved in the enantioselectivity-determining step as in the classical rhodium–diphosphine system.[19] In the present system, hydrogen coordination and oxidative addition to yield an Ir^V complex appear to be the steps in which the selectivity is determined.[20] However, a full theoretical study is needed for a detailed understanding of the present catalytic system and will be reported in the near future.

In summary, we have shown that the MaxPHOX–Ir catalyst system provides the highest selectivity reported to date for the reduction of cyclic enamides derived from α- and β-tetralones, outperforming Ru and Rh catalysts. These results indicate that iridium catalysts can be also proficient in the reduction of alkenes bearing metal-coordinating groups. For the present system, selectivity was pressure-dependent; in most cases, lowering of the hydrogen pressure to 3 bar resulted in an increase in enantioselectivity. Moreover, the process can be carried out in environmentally friendly solvents, such as methanol and ethyl acetate, with no loss of selectivity. The structural diversity of the MaxPHOX ligand template was pivotal for attaining such results.[21]

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[15] CCDC 1471581 (enantiomer of **6g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[16] We believe that during the catalysis the iridium complex is cationic in nature. The reaction conditions are nonbasic. Under such conditions, the P–NH group in the backbone (the acidity of which resembles that of an amido group) will not be deprotonated to provide an anionic ligand. It has been reported that anionic P,N ligands decrease the coordination strength of these substrates, which are generally difficult to fully convert; see: F. W. Patureau, C. Worch, M. A. Siegler, A. L. Spek, C. Bolm, J. N. H. Reek, *Adv. Synth. Catal.* **2012**, *354*, 59.
[17] For theoretical studies on alkene hydrogenation with P,N–iridium complexes, see: a) P. Brandt, C. Hedberg, P. G. Andersson, *Chem. Eur. J.* **2003**, *9*, 339; b) Y. Fan, X. Cui, K. Burgess, M. B. Hall, *J. Am. Chem. Soc.* **2004**, *126*, 16688; c) T. L. Church, T. Rasmussen, P. G. Andersson, *Organometallics* **2010**, *29*, 6769; d) J. Mazuela, P.-O. Norrby, P. G. Andersson, O. Pàmies, M. Diéguez, *J. Am. Chem. Soc.* **2011**, *133*, 13634; e) K. H. Hopmann, A. Bayer, *Organometallics* **2011**, *30*, 2483.
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[20] Although an Ir^{III}/Ir^{V} catalytic cycle is now the commonly accepted mechanism for alkene hydrogenation, the alternative Ir^{I}/Ir^{III} cycle for alkenes with a coordinating group can not be ruled out.
[21] The hydrogenation of alkene **2** with two commercially available [Ir(P,N)(cod)]BAr_F catalysts afforded the product with 80% *ee* or less (see the Supporting Information for full details).

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