Asymmetric Hydrogenation of Seven-membered C=N-containing Heterocycles and Rationalization of the Enantioselectivity

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Abstract: Iridium(I) complexes of phosphine-phosphite ligands efficiently catalyze the enantioselective hydrogenation of diverse seven-membered C=N-containing heterocyclic compounds (eleven examples; up to 97% *ee*). P–OP ligand **L3**, which incorporates an *ortho*-diphenyl substituted octahydrobinol phosphite fragment, provided the highest enantioselectivities in the hydrogenation of most of the heterocyclic compounds studied. The observed sense of stereoselection was rationalized by means of DFT calculations.

Introduction

Many biologically active compounds contain a chiral heterocyclic structural motif.[1] The development of methods to access partly or fully reduced enantiopure heterocycles has increased in scope and importance in recent years. The enantioselective reduction of heterocyclic compounds is becoming more important in the preparation of their partly or fully reduced analogues, as this strategy benefits from a great diversity of starting materials and minimizes the need for manipulation of functional groups during the preparation of target compounds.[2] Transition metal-catalyzed asymmetric hydrogenation has been employed to reduce a large number of nitrogenated heterocyclic compounds (for instance pyridines and other monocyclic nitrogenated derivatives, quinolines, isoquinolines, quinoxalines and related compounds, benzoxazines and related derivatives, indoles, etc.) with high catalytic efficiencies and enantioselectivities. Although nitrogenated seven-membered heterocyclic motifs with stereogenic centers constitute an important pharmacophore,[3] examples of the asymmetric reduction of seven-membered heterocyclic derivatives are scarce in the literature.[4]

We recently reported the hydrogenation of an array of structurally diverse five- and six-membered heterocyclic compounds **1** mediated by iridium(I) complexes of phosphine-phosphite ligands[5] [Ir(Cl)(cod)(P–OP)] with high catalytic activity (Scheme 1).[6] Ligand **L1**, which incorporates an (R_a)-configured [1,1'-binaphthalene]-2,2'-diol phosphite group, provided the highest enantioselectivities in the asymmetric hydrogenation of heterocyclic compounds **1**. Interestingly, we described that the addition of a Brønsted acid (cat. amounts of HCl for 2-alkyl substituted quinolines[6a] and quinoxalines[6a] and stoichiometric amounts of *rac*-camphorsulfonic acid for indoles[6c]) increased the conversion of the hydrogenation reaction and even positively affected the enantioselectivity.[6a] Herein we report on the development of efficient Ir-(P–OP) complexes as catalysts for the enantioselective asymmetric hydrogenation of diversely substituted seven-membered C=N-containing heterocyclic compounds (see structures **3**, **5**, **7**, **9** and **11** in Scheme 1).

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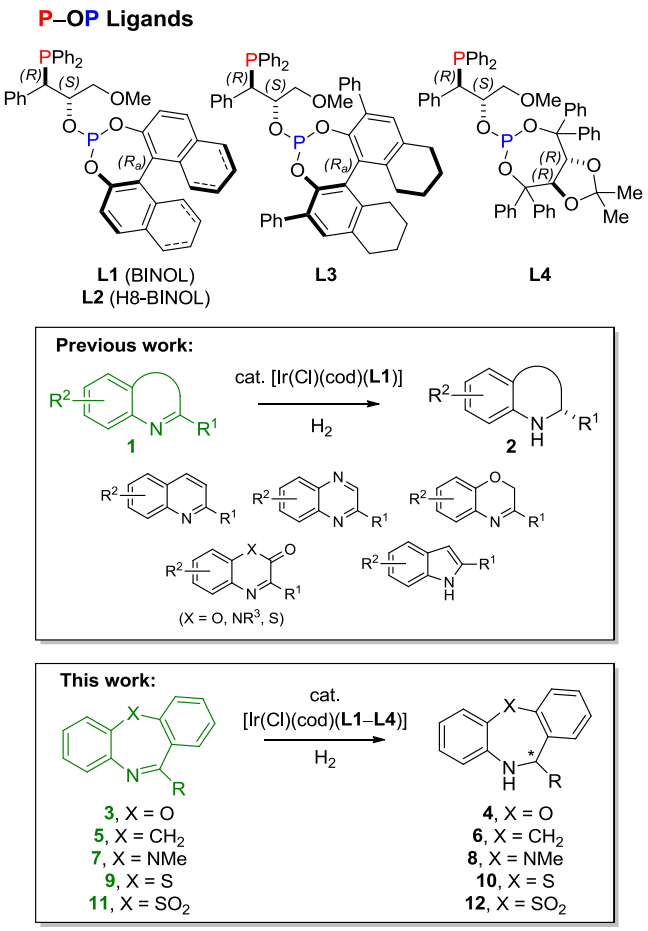


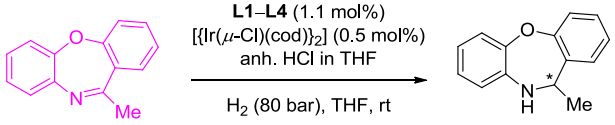
Scheme 1. Enantioselective partial hydrogenation of nitrogenated heterocyclic compounds.

Results and Discussion

Ir-catalyzed asymmetric hydrogenation. Initial screening and optimization

The present work began with the enantioselective hydrogenation of oxazepine **3a** as the model substrate using well-established[6a] in situ prepared iridium complexes of P–OP ligands **L1**–**L4** as pre-catalysts. The reaction conditions employed (1 mol% cat.; [**3a**] = 0.2 M in THF, 80 bar H_2, rt) efficiently led to the hydrogenated product **4a** with complete conversion in the absence of HCl as additive (see entries 1, 3, 5 and 7 in Table 1) with enantioselectivities ranging from 16% *ee* for **L4** to 79% *ee* for **L3**.[7] Enantioselectivities were improved by using 10 mol% HCl in the case of ligands **L1**, **L2** and **L3** (compare entries 1, 3 and 5 with entries 2, 4 and 6 in Table 1), with ligand **L3** providing the highest enantioselectivities (86% *ee*, entry 6 in Table 1). The effects of a set of achiral and enantiomerically pure additives on the hydrogenation of substrate **3a** were also studied.[8] With the exception of HCl, other acid additives scarcely affected the conversion and enantioselectivity of the hydrogenation of this substrate (see Table SI2).[8] Further attempts to optimize the hydrogenation conditions involved varying the amount of HCl (see entry 9 in Table 1) and reducing the temperature (see entry 10 in Table 1). Increasing the amount of additive did not have any effect on the conversion and *ee* (compare entries 6 and 9 in Table 1). The hydrogenation of **3a** was also run at lower temperature (0 ºC instead of rt), based on the premise that lowering the temperature normally offers higher *ee*. As listed in entry 10 of Table 1, the *ee* at 0 ºC was 1% higher than at rt. However, further hydrogenation studies at this temperature were not considered, as conversion was incomplete. The enantioselectivity of the hydrogenation of **3a** was solvent dependent, and 2-methyltetrahydrofuran (MeTHF), dichloromethane (DCM) and toluene led to a noticeable increase in the *ee* of the reaction (compare entries 11, 12 and 13 with entry 6 in Table 1).

Table 1. Asymmetric hydrogenation[a] of **3a** mediated by [Ir(Cl)(cod)(**L1**–**L4**)].



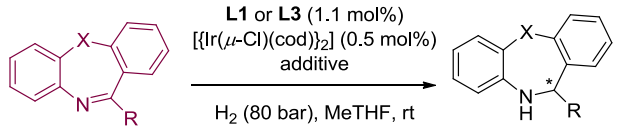
Entry	Ligand	Observations on the reaction conditions	Conv[b]	*ee* (%)[c] (config.)[d]
1	**L1**	No additive	99	42 (*S*)
2	**L1**	10 mol% HCl	99	53 (*S*)
3	**L2**	No additive	99	29 (*S*)
4	**L2**	10 mol% HCl	99	57 (*S*)
5	**L3**	No additive	99	79 (*R*)
6	**L3**	10 mol% HCl	99	86 (*R*)
7	**L4**	No additive	99	16 (*S*)
8	**L4**	10 mol% HCl	99[f]	8 (*S*)
9	**L3**	20 mol% HCl	99	86 (*R*)
10	**L3**	10 mol% HCl; 0 ºC	90	87 (*R*)
11	**L3**	10 mol% HCl, DCM	99	91 (*R*)
12	**L3**	10 mol% HCl, toluene	99	91 (*R*)
13	**L3**	10 mol% HCl, MeTHF[e]	99	91 (*R*)

[a] Reaction conditions: [{Ir(μ–Cl)(cod)}2]/P–OP ligand/substrate = 0.5:1.1:100 for pre-catalyst levels of 1 mol%, respectively, at rt, 20 h and a substrate concentration of 0.20 M in THF. If additive was present, the indicated amount of additive with respect to **3a** was added to a solution of the substrate before adding the catalyst. The values shown are the average of at least two runs. [b] Conversions were determined by ^{1}H NMR. [c] Determined by HPLC analysis using chiral stationary phases. [d] Absolute configuration was assigned by comparison with literature data (see ref. [4c]). [e] MeTHF = 2-methyltetrahydrofuran. [f] The selectivity of the reaction towards **4a** was 35%.

Expanding the substrate scope

Once the optimal hydrogenation conditions for **3a** had been established, the hydrogenation of an array of seven-membered heterocycles was studied. 2-Methyltetrahydrofuran was chosen as the optimal solvent for further studies, given the good results in the hydrogenation of **3a**. The heterocycles studied and the optimal ligand (**L1** or **L3**) for achieving the highest *ee*'s are summarized in Table 2. The results using 10 mol% HCl are only indicated in Table 2 when this additive provided higher conversions and/or *ee*'s. The reader is referred to the Supplementary Information (Table SI3) for complete hydrogenation results employing **L1** and **L3** as ligands and in the absence or presence of anhydrous HCl as additive.

Table 2. Asymmetric hydrogenation[a] of seven-membered *N*-Heterocyclic compounds mediated by [Ir(Cl)(cod)(**L1** or **L3**)].



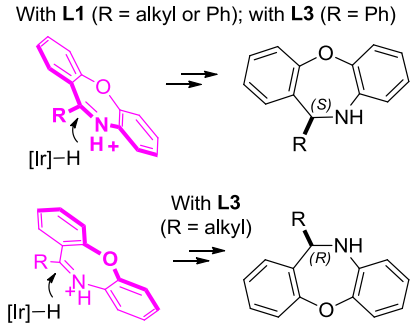
3, **5**, **7**, **9**, **11** — **4**, **6**, **8**, **10**, **12**

Entry	Substrate (X, R)	Ligand	Additive	Conv[b]	*ee* (%)[c] (config.)[d]
1	**3a** (O, Me)[e]	**L3**	10 mol% HCl	99	91 (*R*)
2	**3b** (O, Ph)	**L1**	none	97	83 (*S*)
3	**3c** (O, *i*Pr)	**L3**	none	99	73 (*R*)
4	**3d** (O, Bn)	**L3**	10 mol% HCl	99[f]	87 (*R*)
5	**5a** (CH_2, Me)	**L3**	none	99	70 (*R*)
6	**5b** (CH_2, Ph)	**L3**	10 mol% HCl	33[g]	9 (*S*)
7	**7a** (NMe, Me)	**L3**	10 mol% HCl	99	84 (*R*)
8	**7b** (NMe, Ph)	**L1**	none	24[g]	36 (*S*)
9	**9a** (S, Me)	**L3**	10 mol% HCl	99	91 (*R*)
10	**9b** (S, Ph)	**L3**	none	72[f]	97 (*S*)
11	**11a** (SO_2, Me)	**L3**	10 mol% HCl	99[f]	77 (*R*)

[a] Reaction conditions: [{Ir(μ–Cl)(cod)}2]/P–OP ligand/substrate = 0.5:1.1:100 for pre-catalyst levels of 1 mol%, respectively, at rt, 20 h and a substrate concentration of 0.20 M in MeTHF. If additive was present, the indicated amount of additive with respect to substrate was added to a solution of the substrate before adding the catalyst. The values shown are the average of at least two runs. [b] Conversions were determined by ^{1}H NMR. Isolated yields after chromatography were > 95%, unless otherwise stated. [c] Determined by HPLC analysis using chiral stationary phases. [d] Absolute configurations of **4a**, **4b**, **4d**, **10a** and **10b** were assigned by comparison with literature data (see ref. [4c] for the oxazepines and ref. [4h] for the thiazepines). The configurations of **4c**, **6a**, **6b**, **8a** and **8b** were assumed by analogy. The absolute configuration of **12a** was determined by X-Ray analysis (see SI for details). [e] These results have been already summarized in Table 1, but are included here for comparison. [f] Isolated yields for **4d**, **10b** and **12a** were, 32%, 53% and 59%, respectively. [g] Isolation was not attempted due to low conversions and *ee*'s.

Several trends can be extracted from the results listed in Table 2. Firstly, **L3** was the ligand of choice for heterocycles with R = alkyl group (entries 1, 3–5, 7, 9 and 11 in Table 2). For these substrates, *ee*'s ranged from 70 to 91%, with the highest *ee*'s being obtained for oxazepine **4a** and thiazepine **9a** (91% *ee*; see entries 1 and 9 in Table 2). Secondly, the use of HCl as additive in the hydrogenation of substrates with R being an alkyl group had, with the exception of substrates **3c** and **5a** (see entries 3 and 5 in Table 2), a positive effect on the *ee*'s.[9] Examples of the use of Brønsted acids as substrate activators in iridium-mediated hydrogenations are numerous[2j] however, despite the improvement in catalyst activity and/or selectivity induced by these additives, their role remains in many cases unclear.[2j] The third and last trend that can be seen in the data summarized in Table 2, is that the hydrogenation of the substrates with R = Ph (compounds **3b**, **5b**, **7b** and **9b**) was more complicated than that of their alkyl substituted analogues. Though the hydrogenation of the *O*- and *S*-containing substrates took place efficiently in the absence of HCl (conversions up to 97%, *ee*'s up to 97%, entries 2 and 10 in Table 2), the hydrogenation of carbon and nitrogen-analogues **5b** and **7b** proceeded with low conversions and *ee*'s (entries 6 and 8 in Table 2).

Previous work from our group on asymmetric hydrogenations mediated by Ir-[6] or Rh- complexes[10] of P–OP ligands revealed that the phosphite group was the principal stereochemical director in the reaction (opposite configurations for the resulting hydrogenated products are obtained when the configuration of the phosphite moiety is inverted). Moreover, the introduction of substituents at the 3 and 3' positions of the [1,1'-biaryl]-2,2'-diol group did not change the configuration of the final product in Rh-mediated hydrogenations.[10] Interestingly, ligands **L1** (or **L2**) and **L3**, whose main difference is the presence or absence of substituents at the 3 and 3' positions of the binaphthyl motif, led to opposite enantiomers of **4**, **6** and **8** depending on the nature of the R substituent (alkyl or aryl groups; as an example, see Scheme 2 for the hydrogenation reactions leading to **4**).



Scheme 2. Hydrogenation reactions of **3** leading to products **4.**

Rationalization of the stereochemical outcome of the hydrogenations by DFT calculations

To shed light on the correlation between the features of the P–OP ligands and enantioselection in the hydrogenation towards alkyl-substituted products, we performed a theoretical investigation into the reactivity of the catalytic systems derived from ligands **L1** and **L3** with substrate **3a**. We considered this substrate to be suited to our purposes, as the configuration of the final product depends on whether the substituents at the 3 and 3' positions of the phosphite group are H (**L1**; *S*-configured product, see entries 1 and 2 in Table 1 and Scheme 2) or Ph groups (**L3**; *R*-configured product; see entries 5 and 6 in Table 1 and Scheme 2) and the absolute stereochemistry of its hydrogenated product was unequivocally assigned. Theoretical studies of enantioselective processes usually focus on the stereo-determining step and compare the energy of transition states (TS's) for the paths leading to the *R* and *S* products.[11] The mechanism for the hydrogenation of iminic bonds is complex but has been explored at the experimental and theoretical level by a number of groups.[12] Mechanistic studies from Pfaltz and co-workers have revealed that the employed iridium complexes react with acyclic C=N-containing substrates to form stable cyclometallated iridium complexes that are the real hydrogenation catalysts.[13] Besides, a number of mechanistic studies from other research groups have revealed that the hydrogenation process takes place by transfer of proton and hydride to the C=N bond of the heterocyclic derivative being non-coordinated to the metal center.[14]

We first explored the possibility of the hydrogenation pathway involving the formation of cyclometallated iridium complexes derived from **3a**. The stabilities of the plausible four-membered iridacycles derived from **3a** were computed at the BP86/def2-SVP level of theory (see Figure SI68), which is a good compromise between the size of the system (up to 139 atoms for the iridacycle involving **L3**) and the accuracy of the results (see the SI for a comparison of this functional with MP2 and M06-2X methods). The energy content of the resulting four-membered iridacycles was very high indicating the highly

strained nature of these compounds.[15] Therefore this hydrogenation pathway *via* the formation of such intermediates derived from **3a** was not further explored.[16] As regards the hydrogenation pathway involving proton and hydride transfers to the C=N bond of heterocyclic derivatives, Crabtree and Eisenstein[14b] identified octahedral dihydrido mono-dihydrogen iridium complexes as crucial intermediates in the hydrogenation process. This is because hydrogen transfer from H_2 to the C=N bond starts with proton migration from the dihydrogen ligand to the nitrogen atom. Once the C=N bond is protonated,[17] the position alpha to nitrogen is activated for the subsequent hydride transfer, which is the stereo-determining step (see Scheme 2).

Our own studies[6a] and those of others[5b] have demonstrated that the complexation of P–OP ligands with [{Ir(μ-Cl)(cod)}$_2$] quantitatively leads to compounds [Ir(Cl)(cod)(P–OP)], which correspond to the expected neutral pentacoordinated iridium(I) complexes. Removal of the cod ligand under hydrogenative conditions led to a complex mixture of P–OP-iridium complexes. Unfortunately, neither NMR nor X-Ray analysis allowed us to unequivocally establish the structure of the iridium complexes present in solution (no crystals suitable for X-Ray analysis could be isolated from this mixture). For this reason, the relative stabilities of the plausible [Ir(Cl)(H)$_2$(H–H)(**L1** or **L3**)] complexes were computed at the BP86/def2-SVP level of theory. From among all the possible isomers in an octahedral iridium complex with one bidentate (**L1** or **L3**) and one chlorido ligand, only those with the two hydrido and dihydrogen ligands in a *fac*[18] (facial) geometry were considered.[19] This is because hydrogen transfer from [Ir(Cl)(H)$_2$(H–H)(**L1** or **L3**)] complexes will lead to a trihydrido iridium complex and metal trihydrides have an intrinsic preference[14b] for a *fac* geometry to avoid hydrido ligands that are mutually placed in a *trans* fashion. Interestingly, in [Ir(Cl)(H)$_2$(H–H)(**L1**)] the favorable *fac* isomers (see Figure 1) contain chlorido ligands pointing in the same direction and perpendicular to the plane that contains the P–OP and Ir atoms (see Figure 1a,b). The slightly more favored complex (difference 0.3 kcal·mol^{-1}) has the H–H ligand *cis* to the phosphite group. With regard to [Ir(Cl)(H)$_2$(H–H)(**L3**)], the lowest energy isomers also contain chlorido ligands perpendicular to the same plane but pointing in the opposite direction with respect to the [Ir(Cl)(H)$_2$(H–H)(**L1**)] complexes (see Figure 1c,d). This is due to the formation of intramolecular C–H···Cl bonds (see Figure 1 and SI70). This differentiating feature is very important for rationalizing the opposite enantioselectivity observed for **L1** and **L3** with methyl substituted substrates such as **3a** (vide infra).

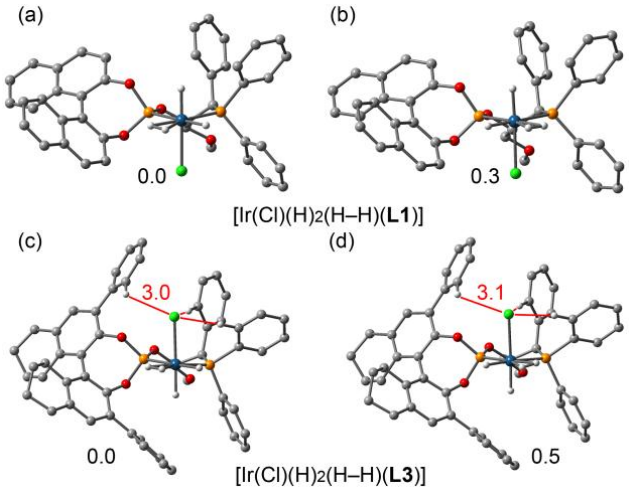


Figure 1. (a-d) Optimized geometries of the most stable isomers of [Ir(Cl)(H)$_2$(H–H)(**L1** or **L3**)] (some H atoms omitted for clarity; distances in Å; energies in kcal·mol^{-1}).

Protonation of **3a** by [Ir(Cl)(H)$_2$(H–H)(**L1** or **L3**)][17] leads to the [H**3a**][Ir(Cl)(H)$_3$(**L1** or **L3**)] assembly (see Figure 2a,b). Both isomers of complex [Ir(Cl)(H)$_2$(H–H)(**L1**)] (see Figure 1a,b) yield the same *fac* trihydrido iridium complex upon proton transfer (same behavior for **L3**), which simplifies the study. Proton transfer is not the stereo-determining step and the configuration of the final product is determined at the later stages of the catalytic cycle. Therefore, we employed calculations for understanding the stereochemical outcome of the reaction from the protonated substrate (H**3a**). Beginning from the initial geometry after proton transfer, where the N–H group points to the Ir–H motif (see Figure 2a,b), we examined different orientations of the protonated substrate (H**3a**) interacting with [Ir(Cl)(H)$_3$(**L1** or **L3**)]. Remarkably, we found a pre-TS complex for each ligand (see Figure 2c,d) that was lower in energy than the initial assembly due to the formation of favorable non-covalent interactions. In the case of **L1**, the preferred arrangement is governed by two interactions that fix the geometry of the substrate (H-bonds and $CH_3\cdots\pi$ interactions, see Figure 2c). This pre-organized complex facilitates the nucleophilic attack of the hydrido group that is located 3.0 Å away from the C atom in the C=N group (pro-(*S*) attack). In the case of **L3**, the presence of the chlorido ligand at the position opposite the P–OP containing plane with respect to **L1** and the formation of a strong N–H···Cl interaction fixes the substrate in a

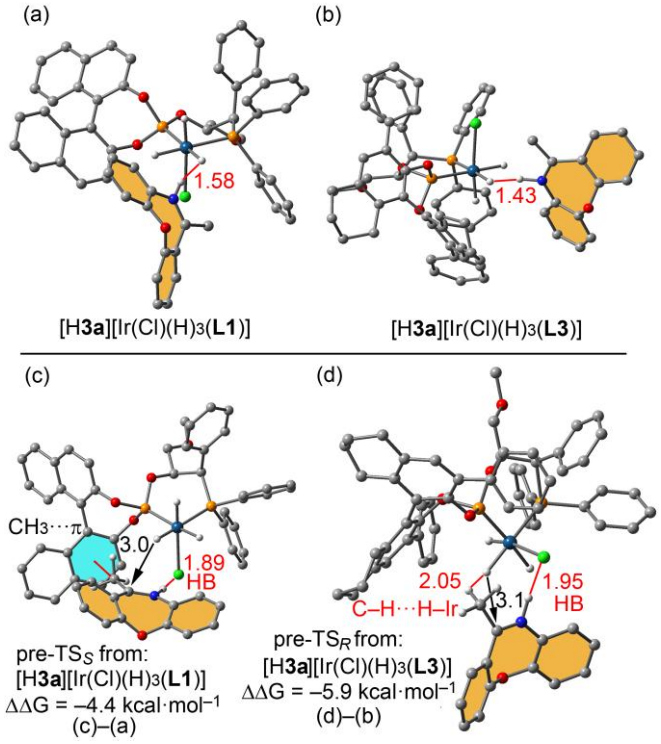


Figure 2. (a,b) Optimized geometries of [H**3a**][Ir(Cl)(H)$_3$(**L1** or **L3**)] assemblies. (c,d) Distances in Å of pre-TS complexes found for [H**3a**][Ir(Cl)(H)$_3$(**L1** or **L3**)] (some H atoms omitted for clarity; distances in Å).

different arrangement compared to **L1**. Moreover the formation of a C–H···H–Ir non-covalent interaction[20] (see Figure 2d) fixes the position of the substrate, facilitating the pro-(*R*) attack of the hydrido ligand (located at 3.1 Å). The pre-TS complexes that would organize the protonated substrate towards the minor enantiomer (i.e. pro-(*R*) attack for **L1** and pro-(*S*) attack for **L3**) were not found in the potential hypersurface. The geometries of the TS's are shown in Figure 3. It is important to note the existence of strong N–H···Cl hydrogen-bonds[21] in the favored TS's. These interactions are crucial in rationalizing the observed sense of stereoselection. The difference in energy between the two TS's states derived from **L1** ($\Delta\Delta G^{\#}$ = 2.2 kcal mol^{-1}) is mainly governed by the different strength of two hydrogen-bond interactions: an N–H···Cl hydrogen-bond for the TS leading to the major enantiomer (TS_S; see Figure 3a) and an N–H···O hydrogen-bond[22] for the TS leading to the minor enantiomer (TS_R; see Figure 3c). Since the N–H···Cl interaction involves an anionic ligand, it is electrostatically favored with respect to the N–H···O interaction. As regards **L3**, the transition state leading to the major enantiomer is also stabilized by an N–H···Cl hydrogen-bond (TS_R; see Figure 3b), whilst that leading to the minor enantiomer is only stabilized by a weaker N–H···π interaction involving a phenyl group (see Figure 3c). Since this N–H··· π interaction involving TS_S derived from **L3** is also weaker than the N–H···O hydrogen bond in TS_R derived from **L1** (both leading to the minor enantiomers of the hydrogenation product of **3a**), the $\Delta\Delta G^{\#}$ value for **L3** (4.3 kcal mol^{-1}) is higher than that for **L1** (2.2 kcal mol^{-1}). This observation is in agreement with the higher enantioselectivity observed experimentally in the hydrogenation of **3a** with **L3** than that with **L1** (compare entry 5 with entry 1 in Table 1, respectively).

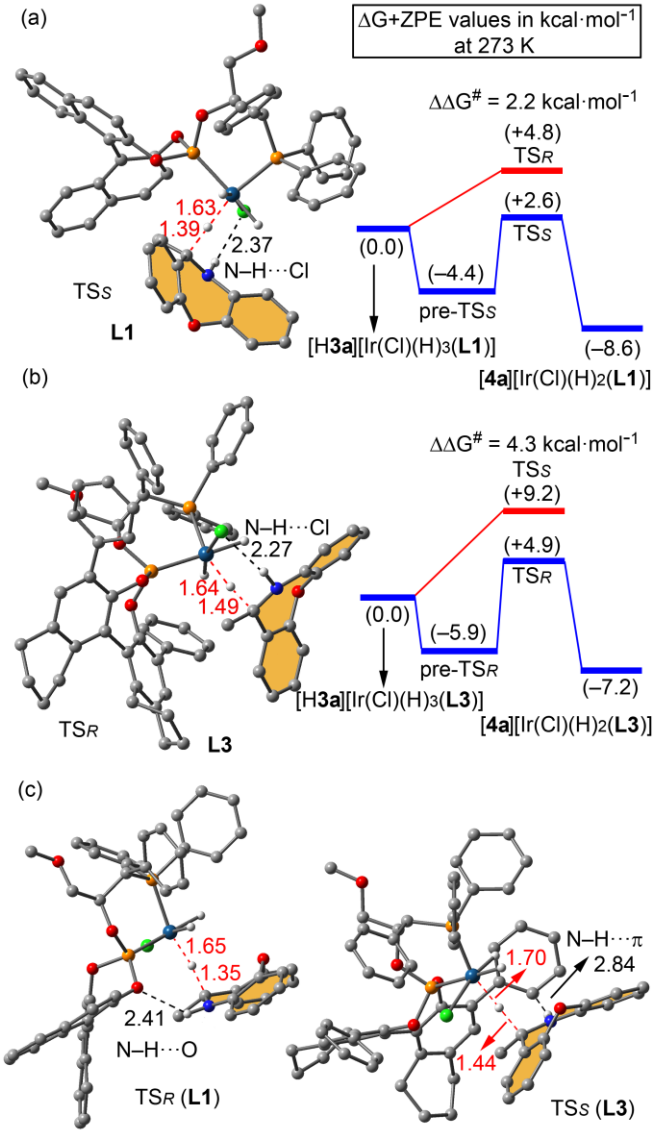


Figure 3. Optimized geometries of the transition states of **L1** (a) and **L3** (b) and their energetic profiles in kcal·mol^{-1} (some H atoms omitted for clarity). (c) optimized structures of the high energy TS's (distances in Å).

Conclusions

In conclusion, catalytic screening in enantioselective hydrogenation reactions indicate that the iridium complexes of chiral P–OP ligands **L1** and **L3** are excellent catalysts in the hydrogenation of various seven-membered heterocycles that contain C=N bonds. The "lead" pre-catalyst for alkyl-substituted seven-membered heterocycles (derived from ligand **L3**) in combination with catalytic amounts of HCl exhibits excellent catalytic properties in this transformation. The hydrogenation of aryl-substituted seven-membered heterocycles was more complicated and highly efficient hydrogenation conditions could only be developed for phenyl substituted oxa- and thia-azepines employing **L1** without any additive. The enantioselectivity has been rationalized by means of DFT calculations, which identified the position of the Cl-ligand in catalytically relevant iridium structures and a number of non-covalent interactions (i.e. N–H···Cl, CH···π and CH···H–Ir interactions[23]) as key features in rationalizing the stereochemical outcome of the reactions with

ligands **L1** and **L3**. We are currently expanding the scope of the hydrogenation reaction mediated by these ligands to new heterocycles and will report on this work in due course.

Experimental Section

General procedure for the Ir-catalyzed asymmetric hydrogenation

A solution of the required amount of [{Ir(μ–Cl)(cod)}$_2$] (0.005 mmol) and the P–OP ligand (0.011 mmol) in the corresponding dry and deoxygenated solvent (5.0 mL) was loaded into an autoclave under N_2, in which the required amounts of substrate (1 mmol) and anhydrous HCl (0.1 M solution in the required solvent), if necessary, were placed beforehand. The concentration of the substrate was adjusted to a final 0.20 M concentration. The autoclave was purged three times with H_2 (at a pressure not higher than the one selected) and finally, the autoclave was pressurized with H_2 to the desired pressure. The reaction mixture was stirred at the desired temperature for the stated reaction time. The autoclave was subsequently depressurized, the reaction mixture passed through a short pad of SiO_2 and further eluted with EtOAc (2 x 1 mL). The resulting solution was evaporated in vacuo. The conversion was determined by ^{1}H NMR and enantioselectivities were determined by HPLC analysis on chiral stationary phases.

Acknowledgements

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Keywords: Enantiopure heterocycles • Asymmetric hydrogenation • Substrate activation • Iridium • Phosphine-phosphites

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[8] For a complete summary on the effects of acid additives, see Table SI2 in the Supporting Information.

[9] See Table SI3 from the Supporting Information for the hydrogenation conditions assayed.

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[15] For the calculated energy contents of the four-membered iridacyles derived from **3a** and their structures, see the Supporting Information (Figure SI68).

[16] The Pfaltz mechanism (reference 13) cannot be excluded for substrates where cyclometallation can be expected to be favored, such as for the arylsubstituted substrates studied in this work.

[17] The use of catalytic amounts of HCl as additive translates to partial protonation of the substrate (HCl is added to the substrate before the catalyst). However, it should be recalled at this point that dihydrogen ligands in iridium complexes might certainly play a role in the protonation of the substrate: most of the heterocycles studied are fully hydrogenated

with high enantioselectivities employing substoichiometric amounts of HCl, or even in the absence of HCl (see Tables 1, SI1, SI2 and SI3).
[18] *Nomenclature of Inorganic Chemistry*, IUPAC recommendations 2005 (Eds.: N. G. Connelly, T. Damhus, R. M. Hartshorn, A. T. Hutton), RSC Publishing, Northampton, **2005**.
[19] In fact, for each ligand we have optimized six possible isomeric iridium complexes (including *mer* complexes, see Figures SI69 and SI70) and the most favorable ones are *fac* isomers.
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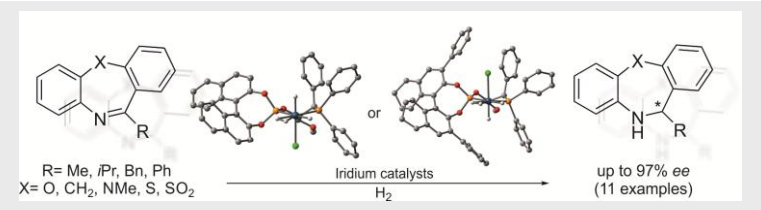

Cl-Switch: Efficient enantioselective hydrogenation of seven-membered *N*-heterocycles mediated by Ir-(P–OP) complexes is described (11 examples, up to 97% *ee*). The position of the Cl ligand in catalytically relevant Ir-species (amongst other factors) is key for rationalizing the stereochemical outcome.

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