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Asymmetric hydrogenation of unprotected indoles using iridium complexes derived from P–OP ligands and (reusable) Brønsted acids†

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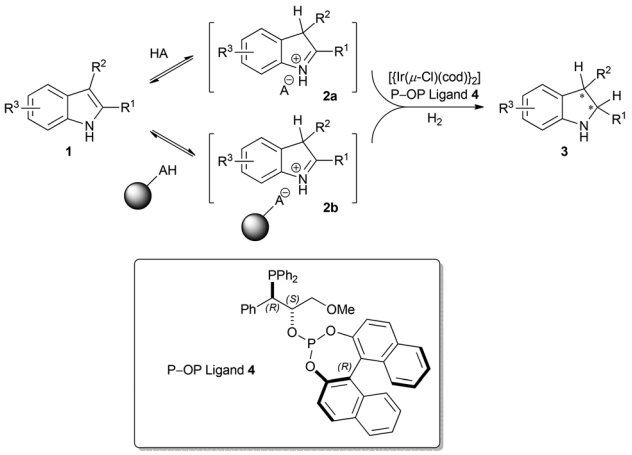
José Luis Núñez-Rico,[a] Héctor Fernández-Pérez[a] and Anton Vidal-Ferran*[a,b]

Unprotected indoles have been efficiently converted to enantiomerically enriched indolines (up to 91% ee) by a stepwise process: (reusable) Brønsted acid-mediated C=C isomerisation and asymmetric hydrogenation using enantioselective iridium catalysts derived from P–OP ligands. This straightforward combination of (reusable) Brønsted acids, which activate the indole ring for hydrogenation by breaking its aromaticity, and enantiomerically pure [Ir(P–OP)]$^+$ complexes as hydrogenation catalysts affords the resulting indolines with high enantioselectivities.

Introduction

Many valuable biologically active compounds contain a chiral indoline structural motif.[1] Among the various synthetic methods developed to obtain enantiomerically pure indolines,[2] direct enantioselective reduction of the corresponding indoles is one of the simplest, most practical and most atom-efficient. Rhodium,[3] ruthenium,[4] and iridium[5] complexes have been reported as efficient catalysts for the asymmetric hydrogenation of N-protected indoles. In contrast, the hydrogenation of unprotected indoles remains scarcely studied, mainly due to catalyst deactivation upon binding of the indole NH group to the metal centre and to the absence of a secondary coordinating group at the N-atom.[6] An important breakthrough in this chemistry was recently achieved by Zhou, Zhang, and co-workers,[7] who developed a strategy based on the use of Brønsted acids as activators. These acids break the aromaticity of the indole ring[8] by generating the iminium ion **2a** (Scheme 1), which is hydrogenated with Pd complexes derived from enantiomerically pure diphosphine ligands.[7] The scope of this methodology was successfully expanded to an array of mono- and disubstituted indoles.[9] Chiral organocatalysts have also been efficiently applied in the hydrogenation of indole derivatives using the same activation strategy.[10] Although these examples enabled efficient asymmetric hydrogenation of unprotected indoles, several practical challenges remain: stoichiometric amounts of a Brønsted acid are required, which calls for its recycling and reuse; and relatively high catalyst loadings are used (2 mol% of Pd catalyst and 10 mol% of organocatalyst; see ref. 7 and 10, respectively).



Scheme 1 Homogeneous and heterogeneous strategies for the Brønsted acid/Ir-mediated asymmetric hydrogenation of unprotected indoles.

Following our previous work on the design and development of efficient iridium-based catalysts derived from enantiomerically pure P–OP ligands[11] for the enantioselective hydrogenation of diversely substituted C=N-containing heterocycles,[11g,12] we report herein our initial efforts in the asymmetric hydrogenation of unprotected indoles by using (easily recyclable and reusable) Brønsted acids together with optically pure iridium complexes derived from our P–OP ligands.[13]

[a]*Institute of Chemical Research of Catalonia (ICIQ), Avgda. Països Catalans 16, E-43007 Tarragona, Spain. E-mail: avidal@iciq.cat; Fax: +34 977920228; Tel: +34 977920210*

[b]*Catalan Institution for Research and Advanced Studies (ICREA), Passeig Lluís Companys 23, E-08010 Barcelona, Spain*

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Results and discussion

The present work began with hydrogenation of 2-methyl-1*H*-indole (**1a**) as a model substrate. Catalytic studies of the asymmetric hydrogenation of indole **1a** were done using the iridium complex derived from ligand **4**, which, in previous studies, exhibited the highest catalytic performance in the hydrogenation of an array of diversely substituted C=N-containing heterocycles.[12] Hydrogenation of **1a** under standard screening conditions (1 mol% *in situ* generated iridium pre-catalyst, 80 bar of H_2 at room temperature in THF) in the absence of any additive proceeded only with low conversion (*ca.* 10%, see entry 1, Table 1). Further studies dealt with the hydrogenation of indole **1a** in the presence of Brønsted acids as additives. Interestingly, addition of one equivalent[14] of such additives (see Table 1) increased the conversion as a function of the strength of the acid: whilst carboxylic acids brought the conversion up to *ca.* 20% (entries 2 and 3, Table 1), their stronger sulfonic acid analogues increased the conversion up to *ca.* 80% (entries 7–11, Table 1). Conversions achieved using phosphoric acid derivatives (up to *ca.* 60% conversion, entries 4–6 in Table 1) lie between those obtained using carboxylic or sulfonic acids. Thus, the lower the pK_a of the additive (pK_a RSO_3H < pK_a $(RO)_2P(=O)OH$ < pK_a RCOOH), the higher the conversion becomes. This observation is in agreement with the proposed activation mechanism for indole hydrogenation: as the acid strength increases (or pK_a decreases), the equilibrium shifts towards the non-aromatic iminium ion **2a**, from which the hydrogenation product **3a** derives.

Interestingly, enantioselectivities were not affected by the additives: in all cases they remained at *ca.* 90% ee. Furthermore, the lack of effect of enantiomerically pure additives in the configuration of the final product or in its enantioselectivity (compare entries 5 and 6 in Table 1 for the effects of (*R*)- and (*S*)-BNP, and entries 10 and 11 for those of the two enantiomers of camphorsulfonic acid [D-(+)- and L-(−)-CSA]) confirms that the additive is not involved in the stereodifferentiating processes during hydrogenation.

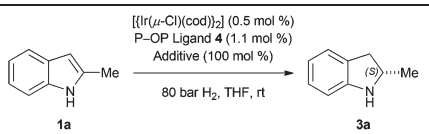
Based on the results of the aforementioned optimisation process (Table 1), it was concluded that racemic camphorsulfonic acid (*rac*-CSA) was the optimal additive, as it simultaneously provided the highest conversion and enantioselectivity.

The next parameter to be explored was the solvent. The effects of different solvents (Table 2) on the catalytic activity of the iridium complex derived from ligand **4** were studied and found to markedly influence the catalyst performance. The highest conversion was accomplished with dimethyl carbonate (DMC), although at the expense of a slight decrease in the enantioselectivity (entry 7 in Table 2). 2-Methyltetrahydrofuran (2-Me-THF), considered to be a green alternative to hazardous solvents in organometallic reactions (by virtue of its production from renewable sources and low water miscibility),[15] proved to be the best solvent, as it gave high conversion (92%) and the highest enantioselectivity (91% ee) (see entry 5 in Table 2). Next, the reaction time was ascertained. However, extending the time did not lead to any noticeable effects on activity. Finally, the catalyst loading was evaluated. At lower loadings, the conversions dropped considerably and the original value (1 mol%) was maintained.

Once the optimal hydrogenation conditions for **1a** had been established, an array of diversely substituted indoles (compounds **1b–f**) was hydrogenated. The results are summarised in Table 3.

The iridium complex derived from ligand **4** exhibited a good catalytic profile (good to high yields and ee's) for all the tested indoles. The chain length of the R^1 group barely influenced the catalytic activity, as evidenced by the fact that the

Table 1 Effects of the additives in the asymmetric hydrogenation of **1a**[a]



1a 3a

Entry	Additive	Conv.[b] (%)	ee[c] (%) (config.)[d]
1	—	11	nd
2	PhCOOH	17	90 (*S*)
3	CF_3COOH	23	90 (*S*)
4	$(PhO)_2P(=O)OH$	49	90 (*S*)
5	(*R*)-BNP[e]	55	89 (*S*)
6	(*S*)-BNP[e]	57	89 (*S*)
7	*p*-Me–C_6H_4–SO_3H (TsOH)	69	88 (*S*)
8	$MeSO_3H$ (MsOH)	81	88 (*S*)
9	*rac*-CSA[f]	83	90 (*S*)
10	D-(+)-CSA[f]	80	90 (*S*)
11	L-(−)-CSA[f]	81	90 (*S*)

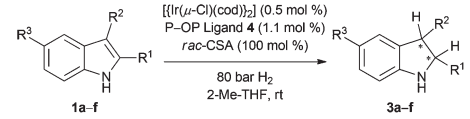
[a] Reaction conditions: *in situ* formed pre-catalyst, [{Ir(μ-Cl)(cod)}$_2$]/P–OP ligand **4**/additive/**1a** molar ratio = 0.5 : 1.1 : 100 : 100, 80 bar H_2, rt, 20 h, 0.2 M in THF. [b] Conversion determined by ^{1}H NMR. [c] Enantiomeric excess determined by HPLC on chiral stationary phases. [d] Absolute configuration was assigned by comparison with reported data. [e] Phosphoric acid derivatives derived from (*R*)- and (*S*)-BINOL ([1,1′-binaphthalene]-2,2′-diol), respectively. [f] D-(+)-Camphorsulfonic acid ((1*S*,4*R*)-7,7-dimethyl-2-oxo-bicyclo[2.2.1]-heptane-1-methanesulfonic acid) and its enantiomer L-(−)-CSA) and racemic forms (*rac*-CSA).

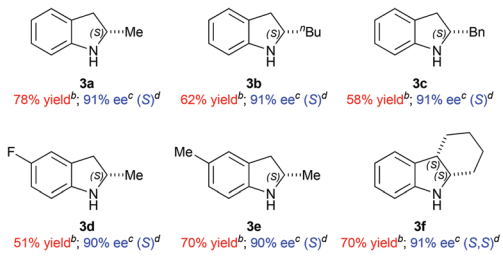
Table 2 Effects of the solvents in the asymmetric hydrogenation of **1a**[a]

Entry	Solvent	Conv.[b] (%)	ee[c] (%) (config.)[d]
1	THF	83	90 (*S*)
2	DCM	99	82 (*S*)
3	IPA	91	86 (*S*)
4	MeOH	81	70 (*S*)
5	2-Me-THF	92	91 (*S*)
6	EtOAc	94	86 (*S*)
7	Dimethyl carbonate (DMC)	>99	84 (*S*)
8	2-Methyl-2-butanol	84	86 (*S*)
9	Diisopropyl ether	64	83 (*S*)
10	DME	91	88 (*S*)

[a] Reaction conditions: *in situ* formed pre-catalyst, [{Ir(μ-Cl)(cod)}$_2$]/P–OP ligand **4**/*rac*-CSA/**1a** molar ratio = 0.5 : 1.1 : 100 : 100, 80 bar H_2, rt, 20 h, 0.2 M in the stated solvent. [b,c,d] See the corresponding footnotes in Table 1.

Table 3 Asymmetric hydrogenation of indoles **1a–f**[a]





[a] Reaction conditions: *in situ* formed pre-catalyst, [{Ir(μ-Cl)(cod)}$_2$]/P–OP ligand **4**/*rac*-CSA/**1a–f** molar ratio = 0.5 : 1.1 : 100 : 100, 80 bar H_2, rt, 20 h, 0.2 M in 2-Me-THF. [b] Isolated yields. Conversions (determined by ^{1}H NMR analysis): 92% for **1a**, 85% for **1b**, 67% for **1c**, 55% for **1d**, 94% for **1e** and 80% for **1f**. [c,d] See the corresponding footnotes in Table 1.

enantioselectivity remained high for the 2-alkylsubstituted indolines **3a** and **3b**. In the case of substrate **1c**, which incorporates a benzyl substituent, the yield was slightly lower, although the enantioselectivity remained high (91% ee). Indoles **1d** and **1e** were each hydrogenated with high enantioselectivity regardless of the electronic nature of the substituents on the benzene ring, although the conversion decreased when an electron-withdrawing group was located at C5 (*i.e.* a fluoro group in **1d**). Moreover, hydrogenation of the 2,3-disubstituted compound **1f** was efficient, yielding the *cis*-indoline **3f** with 91% ee.

Based on these encouraging results, it was then decided to devise a more sustainable variation of this chemistry in which the additive could be reused. Since the hydrogenation reaction required the utilisation of one equivalent of *rac*-CSA as an additive, the use of a solid-supported equivalent of *rac*-CSA (see Scheme 1), which could be easily recovered, recycled and reused once the hydrogenation had finished, was envisaged in this new and greener strategy. Ion-exchange resins incorporating sulfonic acids as functional groups (*e.g.* Amberlyst™, Amberlite™, or DOWEX™ type resins) were the logical choice.

In catalytic studies on the hydrogenation of 2-methyl-1*H*-indole (**1a**) as a model substrate (80 bar of H_2, THF, rt) using 1 mol% of the standard iridium pre-catalyst and different acidic resins,[16] the DOWEX™ 50WX8 resin gave the best results with a notable ee of 90% (entry 1, Table 4). However, the conversion was lower (37%) than that obtained for the analogous homogeneous reaction (entry 7, Table 1), even after extending the reaction time to ensure the diffusion of the reagents through the mesoporous structure of the resins.[16]

In order to determine optimum reaction conditions, several experimental parameters were studied. The results are shown in Table 4.

Upon increasing the reaction temperature from rt to 45 °C, the conversion increased from 37 to 68%, although the

Table 4 Asymmetric hydrogenation of indole **1a** using the DOWEX™ 50WX8 resin as an additive[a]

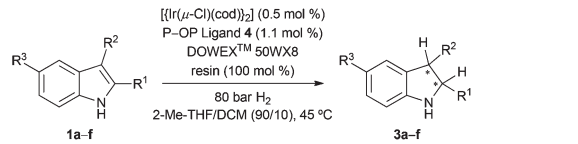
Entry	Solvent	Reaction conditions	Conv.[b] (%)	ee[c] (%) (config.)[d]
1	THF	rt, 65 h	37	90 (*S*)
2	THF	45 °C, 40 h	68	85 (*S*)
3	THF–DCM (90/10)	45 °C, 40 h	72	86 (*S*)
4	2-Me-THF	45 °C, 40 h	66	87 (*S*)
5	2-Me-THF–DCM (90/10)	45 °C, 48 h	87	87 (*S*)
6[e]	2-Me-THF–DCM (90/10)	45 °C, 48 h	83	87 (*S*)
7[e]	2-Me-THF–DCM (90/10)	45 °C, 48 h	81	87 (*S*)

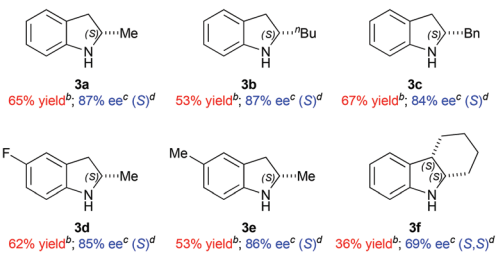
[a] Reaction conditions: *in situ* formed pre-catalyst, [{Ir(μ-Cl)(cod)}$_2$]/P–OP ligand **4**/DOWEX™ 50WX8/**1a** molar ratio = 0.5 : 1.1 : 100 : 100, 80 bar H_2, 0.2 M in the stated solvent. [b,c,d] See the corresponding footnotes in Table 1. [e] The DOWEX™ 50WX8 resin was recovered, suspended in aq. HCl (10%), briefly stirred, filtered, washed, dried and reused two more times (see entries 6 and 7 for the results of the second and third cycles of reused catalyst and ESI for details).

enantioselectivity was slightly lower (compare entries 1 and 2 in Table 4). The use of 2-Me-THF as a solvent gave the highest enantioselectivity (entry 4 in Table 4), and addition of a 10% volume amount of dichloromethane as a co-solvent increased the conversion (see entry 5 in Table 4) to a level similar to that under the homogeneous activation/hydrogenation conditions. Interestingly, the DOWEX™ 50WX8 resin used in this experiment as the additive was recovered, recycled and reused up to two times (entries 6 and 7 in Table 4) giving comparable catalytic activity.

The scope of these newly developed hydrogenation conditions was further tested using the same array of substituted indoles (**1a–f**) as before (Table 5). Gratifyingly, under these conditions the catalytic performance of the [Ir(P–OP)] catalyst was comparable to that observed with sulfonic acids in

Table 5 Asymmetric hydrogenation of indoles **1a–f** using the DOWEX™ 50WX8 resin as an additive[a]





[a] Reaction conditions: *in situ* formed pre-catalyst, [{Ir(μ-Cl)(cod)}$_2$]/P–OP ligand **4**/DOWEX™ 50WX8/**1a–f** molar ratio = 0.5 : 1.1 : 100 : 100, 80 bar H_2, 45 °C, 48 h, 0.2 M in 2-Me-THF–DCM (90/10 v/v). [b] Isolated yields. Conversions (determined by ^{1}H NMR analysis): 86% for **1a**, 83% for **1b**, 83% for **1c**, 71% for **1d**, 78% for **1e** and 44% for **1f**. [c,d] See the corresponding footnotes in Table 1.

solution (compare Table 3 with Table 5), with the exception of substrate **1f**, wherein a lower ee value is obtained with the resin as an additive.

Conclusions

In summary, a catalytic enantioselective synthesis of an array of diversely substituted indolines has been developed and optimised. It is based on asymmetric hydrogenation of indoles using enantiomerically pure iridium complexes (derived from P–OP ligand **4**) as pre-catalysts and stoichiometric amounts of sulfonic acids as additives. The best results were obtained using the environmentally benign solvent 2-Me-THF. The present study also provides an efficient method to transform indoles into enantioenriched indolines by a greener hydrogenation method that involves the use of reusable heterogeneous additives (solid-supported sulfonic acids). Results are comparable to those obtained with the homogeneous catalyst.

To the best of the authors' knowledge, the present work constitutes the first example of the use of enantiomerically pure iridium complexes in the asymmetric hydrogenation of unprotected indoles. Furthermore, the disclosed method enables a 50% reduction in the amount of required catalyst relative to similar chemistry (use of enantiomerically pure palladium catalysts). This strategy is presently being extended for the asymmetric hydrogenation of other types of C=N containing heterocycles.

Experimental section

General procedure for the Ir-mediated asymmetric hydrogenation

A solution of the required amount of iridium precursor ($[\{Ir(\mu\text{-}Cl)(cod)\}_2]$) (0.00125 mmol) and the P–OP ligand **4** (0.00275 mmol) in the corresponding dry and deoxygenated solvent (0.75 mL) was added under N_2 into an autoclave containing the substrate (0.25 mmol) and the additive (0.25 mmol) in the deoxygenated solvent (0.5 mL). In all cases the molar concentration of the substrate in the reaction medium was adjusted to a final concentration of 0.20 M. The autoclave was purged three times with H_2 (at a pressure that did not exceed the selected one) and finally, the autoclave was pressurised with H_2 at the desired pressure. The reaction mixture was stirred at the desired temperature for the stated reaction time. After the hydrogen had been carefully released, the resulting mixture was concentrated under vacuum and then treated with saturated $NaHCO_3$ (4 mL). After stirring for 10 min, the mixture was extracted with EtOAc (2 × 4 mL), dried over $MgSO_4$, filtered through a short pad of SiO_2 and, finally, concentrated *in vacuo*. Conversions were determined at this point by ^1H NMR analysis. The hydrogenation products were isolated after chromatography on SiO_2. The enantioselectivities were determined by HPLC analysis on chiral stationary phases and the configuration of the products was established by comparison with reported HPLC data on chiral stationary phases (see ESI† for details).

Acknowledgements

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14 The effect of the amount of additive on the conversion was studied in the hydrogenation of **1a** using TsOH as an additive. The highest conversion was observed when one equivalent of TsOH was used. Catalytic or substoichiometric amounts of this compound led to lower conversions than those obtained for stoichiometric amounts (for the complete set of results, see ESI†). Amounts of TsOH higher than one equivalent were not studied.

15 See, for example: V. Pace, *Aust. J. Chem.*, 2012, **65**, 301 and the references cited therein.

16 Before use, all the resins (Amberlyst™, Amberlite™, and DOWEX™ resins) were first dried and titrated to determine the concentration of acidic groups (equiv. of sulfonic groups per gram of resin). For the complete set of results, see ESI.†