Asymmetric Hydrogenation *vs* Transfer Hydrogenation in the Reduction of Cyclic Imines

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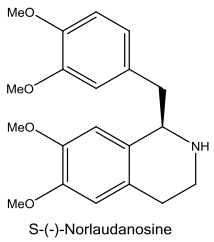
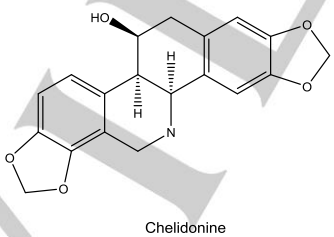
Abstract: A comparison between the two most common reduction approaches for obtaining chiral amines, asymmetric hydrogenation (AH) *versus* asymmetric transfer hydrogenation (ATH), was accomplished by using iridium complexes based on atropoisomeric diphosphines and cyclic diamines as ligands respectively. Seven substrates, different in electronic and steric properties, were screened applying both reduction methods. For AH the best results in terms of enantioselectivity (e.e. up to 64%) were obtained by using [Ir(COD)(TetraMe-BITIOP)]Cl in the presence of DCDMH as additive. ATH was carried out with [IrCp*(CAMPY)Cl]Cl as catalyst, allowing the obtainment of the products with appreciable e.e. (up to 76%).

Introduction

Enantiopure amines are key functionalities in many biologically active molecules. For this reason, extensive efforts are made with the aim to develop an efficient and practical method of their preparation.[1] Although a plethora of approaches is reported for their synthesis, the asymmetric metal-catalysed reduction of imine precursors is considered as an industrially valuable process. Asymmetric Hydrogenation (AH) exploits the use of organometallic complexes bearing chiral atropoisomeric diphosphines as catalysts and it is still a very efficient approach to obtain optically enriched amines.[2] The introduction of transition metal complexes based on chiral 1,2-diamines, and in particular Ts-DPEN and its derivatives,[3] it was possible to skip gaseous hydrogen and to use of a different hydrogen donor such as HCOOH, HCOONa, azeotropic mixture 5:2=TEA:HCOOH or *i*PrOH. These catalytic systems proved extremely efficient in the asymmetric transfer hydrogenation (ATH) of ketones and alkenes, but only in few cases it was applied to the challenging reduction of imines affording high enantioselectivity.[4]



S-(-)-Norlaudanosine



Chelidonine

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Figure 1. Example of alkaloids with pharmacological properties.

Despite the achievements made in this field,[5] the asymmetric reduction of cyclic imines, such as dihydroquinolines, isoquinolines and quinolines, important pharmaceutical intermediates for the production of complex alkaloids and unnatural β-amino acids, is still an unmet goal, thus proving the need for further investigations. [6] (Figure 1)

In the context of this study, in which the two reduction methods resulted comparable or/and complementary, we decided to take into consideration two different isoquinolines, **A** and **B**, the salsolidine precursor **C,** as standard substrate for 3,4-dihydroquinolines, its derivatives **D** and **E**, the quinoline **F** and the sulfonyl imine **G**. (Figure 2)

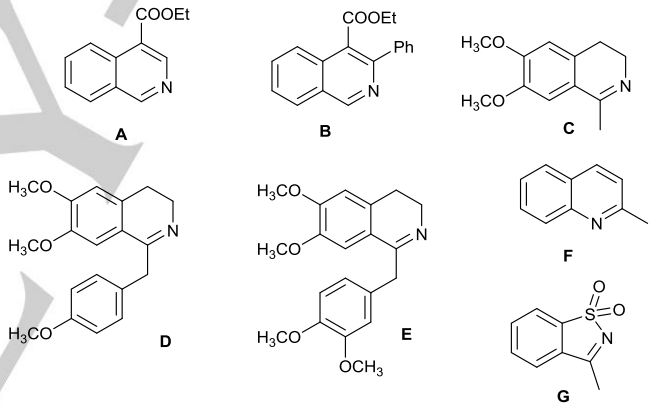


Figure 2. Different evaluated cyclic imines

AH reactions were evaluated using Ir(I) cyclooctadiene complex bearing a chiral basic atropoisomeric diphoshine in the presence of H_2, while for ATH reactions, [Ir(III)Cp*L_2] complexes were employed as catalysts, in which L_2 is a rigid chiral diamine. Moreover, in both AH and ATH, the effect on reactivity and selectivity of different substrates was evaluated and remarkably all the ATH reactions were conducted in different aqueous buffers, thus avoiding the use of organic solvents.

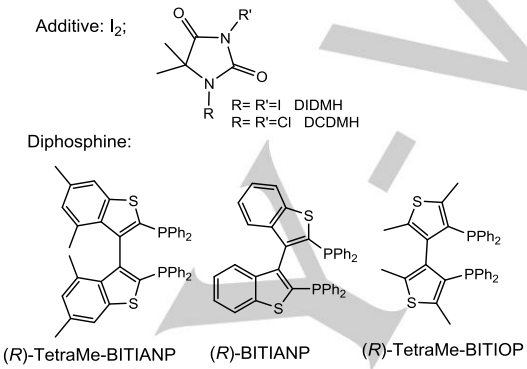
Results and Discussion

Recently, the efficient enantioselective hydrogenation of different 3,4-disubstituted isoquinolines employing an iridium catalyst in association with atropoisomeric ligands and in the presence of a halogen-activator is reported.[7] These substituted hydantoins are known to have a critical role in the catalytic cycle of the catalyst.[8] the above mentioned system bearing as ligand the atropoisomeric diphosphine (*R*)-Synphos is able to reduce these substrates in excellent yield and with modest to excellent

enantioselectivity based on the electronic and steric properties of the molecules. Taking into account these results, we decided to investigate the potential ability of the more basic members[9] of the class of diphosphines in the reduction of the iminic substrates **A, B** and **C**, this last one as standard substrate for 3,4-dihydroquinolines. These diphosphines are derived from the condensation of the thiophene ring, like TetraMe-BITIANP, BITIANP and TetraMe-BITIOP.[10] The two 3,4-disubstituted isoquinolines were chosen considering the possible application of the corresponding tetrahydroquinolines as unnatural β-aminoacids and considering that in the case of substrate **A**, a biocatalytic resolution of the corresponding amines is easy to realize conversely to the more difficult of derivative **B**.[6c, 6d]

Table 1. AH of cyclic imines using the selected atropoisomeric ligands.

Entry	Diphosphine	Substrate	Conversion %[a]	e.e. %
1	(*R*)-TetraMe-BITIANP	**A**	99	14 (*S*)
2	(*R*)-BITIANP	**A**	99	20 (*S*)
3	(*R*)-TetraMe-BITIOP	**A**	99	54 (*S*)
4	(*R*)-TetraMe-BITIANP	**B**	99	29 (*S*, *R*)
5	(*R*)-BITIANP	**B**	99	32 (*S*, *R*)
6	(*R*)-TetraMe-BITIOP	**B**	99	51 (*S*, *R*)
7[b]	(*R*)-Synphos	**B**	98	64 (*S*, *R*)
8	(*R*)-TetraMe-BITIANP	**C**	99	23 (*S*)
9	(*R*)-BITIANP	**C**	99	37 (*S*)
10	(*R*)-TetraMe-BITIOP	**C**	99	63 (*S*)
11	(*R*)-TetraMe-BITIOP	**D**	60	60 (*S*)
12	(*R*)-TetraMe-BITIOP	**E**	68	45 (*S*)



13[c]	(*R*)-TetraMe-BITIOP	**F**	96	64 (*R*)
14	(*R*)-TetraMe-BITIOP	**G**	traces	86[d]

Reactions were conducted with 0.16 M solution substrate using 1 mol % iridium complex in toluene in the presence of DCDMH as additive (substrate:additive = 10:1) at 50°C and 10 atm of H_2 pressure for 24 h. [a] Conversion was obtained by HPLC using correction factor of 1.32 for **A** and 1.23 for **F** and **G** at λ = 283 nm and 220 nm.[11] For product **G** d.e. >99% (*syn*). [b] Data reported in literature.[8a] [c] Reaction conducted in THF at room temperature.[12] [d] See the experimental section for HPLC conditions.

As evinced in the Table 1 for all the substrates, the reduction proceeded from moderate to complete conversion. Different additives such as I_2, 1,3-diiodo-5,5-dimethyl-hydantoin (DIDMH) or 1,3-dichloro-5,5-dimethyl-hydantoin (DCDMH).[13], different solvents, such as THF, DMC and toluene and different reaction conditions (H_2 pressure and temperature) were evaluated (data not reported).

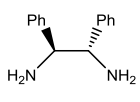
As expected, an increase of the enantioselectivity was observed when the hydrogenation was conducted in the presence of TetraMe-BITIOP, the more basic diphosphine used, which is the best one for the enantioselective reduction of many substrates, resulting in 54% e.e. for **A** (Table 1, entry 3), 51% e.e. for **B** (Table 1, entry 6) and 63% e.e. in the reduction of **C** (Table 1, entry 10). It is worth noting that in the case of substrate **B** the reaction proceeded with excellent diastereoselectivity affording only *syn* diastereomers (d.e. > 99%). The results obtained in the presence of TetraMe-BITIOP are similar to those obtained with Synphos (Table 1, entry 7) considering the comparable electronic properties. In contrast, the more acid ligands, BITIANP and TetraMe-BITIANP, provided lower enantioselectivity.[14]

The optimised protocol for the AH in the chosen substrates consists of $[Ir(COD)Cl]_2$/TetraMe-BITIOP as catalyst, DCDMH as additive and toluene at 50°C for 24 h under 10 atm of H_2. With the aim to expand the substrates diversity for AH, other four imines were investigated different in electronic and steric properties: two dihydroisoquinolines **D** and **E**, precursors of higenamine and norlaudanosine respectively, the quinaldine **F** and the sulfonyl imine **G** derived from saccharine. [5c, 6f, 6g, 15] In particular for substrate **D** a good 60% e.e. was obtained even if the reaction proceeded with a formation of a by-product, easily removed by an acid-base work-up procedure.[6g] When the steric hindrance increased, as in the case of substrate **E**, the enantioselectivity decreased to a modest 45%. For both the **C** derivatives, the reaction did not raise the complete conversion in 24 h (Table 1, entries 11 and 12). In the case of substrate **F**, the best results were obtained again with DCDMH as the additive but the best reaction conversion and enantioselectivity were obtained using THF as solvent at room temperature (Table 1, entry 13). Changing completely the electronic properties of the imine, the reduction of substrate **G** did not proceed (Table 1, entry 14), underlining that the AH of this active imines gave good results only in presence of Pd(II)complexes as pre-catalysts.[16]

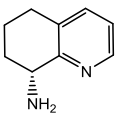
While the 3,4-dihydroisoquinoline is often used as standard substrate for ATH considering their intrinsic electronic properties, quinolines and isoquinolines are less investigated. It is well-known that Noyori-Ikariya complex containing Ts-DPEN as diamine ligand proved the catalyst of choice for the asymmetric transfer hydrogenation not only of ketones but also of imines.[3d, 17] The search for an alternative to this tosylated diamine as source of chirality in transition metal complexes led our research group to synthesise two cyclic diamines that feature both the rigidity and the basicity of Ts-DPEN, even if not tosylated.[18] These ligands called CAMPY, and its 2-methyl derivative, Me-CAMPY, have been successfully applied as ligands in iridium(III)-Cp* complexes for the ATH of substituted ketones providing good results in terms of yield and selectivity.[19] Starting from these encouraging premises, these catalysts were applied initially for screening the reaction conditions to the reduction of **C** using as well as reference ligand the free amine diphenylethylenediamine (DPEN) in an analogue iridium(III)-Cp* complex for a better comparison. The main advantage offered by this catalytic system is the possibility to operate under green conditions. In fact, the stability of the synthesised catalysts in an aqueous reaction environment or in a green solvent (*i*PrOH) prompted us to carry out the reaction under mild reaction conditions avoiding the use of an inert atmosphere and using different buffers (acetate pH 5, MES pH 6, MOPS pH 7, MOPS pH 8).

Table 2. ATH of different cyclic imines in buffer.

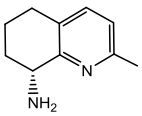
Ligand:



(*S,S*)-DPEN



(*S*)-CAMPY



(*S*)-Me-CAMPY

Entry	Ligand	Substrate	pH	Conversion %[b]	e.e.%

1	(*S*,*S*)-DPEN	**C**	7	42	21 (*S*)
2	(*S*)-Me-CAMPY	**C**	7	99	43 (*S*)
3	(*S*)-CAMPY	**C**	6	99[b]	74 (*S*)
4	(*S*)-CAMPY	**C**	7	99[b]	76 (*S*)
5	(*S*)-CAMPY	**C**	8	99[b]	74 (*S*)
6	(*S*)-CAMPY	**A**	6	87[c]	-
7	(*S*)-CAMPY	**A**	7	85[c]	-
8	(*S*)-CAMPY	**A**	8	22[c]	-
9	(*S*)-CAMPY	**B**	6	-	-
10	(*S*)-CAMPY	**B**	7	34	72 (*S*,*R*)
11	(*S*)-CAMPY	**B**	8	28	41 (*S*,*R*)
12	(*S*)-CAMPY	**D**	6	82	35 (*S*)
13	(*S*)-CAMPY	**D**	7	85	38 (*S*)
14	(*S*)-CAMPY	**D**	8	84	30 (*S*)
15	(*S*)-CAMPY	**E**	6	99	42 (*S*)
16	(*S*)-CAMPY	**E**	7	96	52 (*S*)
17	(*S*)-CAMPY	**E**	8	95	43 (*S*)
18	(*S*)-CAMPY	**F**	6	65	45 (*R*)
19	(*S*)-CAMPY	**F**	7	62	53 (*R*)
20	(*S*)-CAMPY	**F**	8	29	42 (*R*)
21	(*S*)-CAMPY	**G**	6	99	61[d]
22	(*S*)-CAMPY	**G**	7	99	62[d]
23	(*S*)-CAMPY	**G**	8	89	58[d]

All reactions were carried out for 18 h at 20°C using 1 mol % iridium complex in 1.2 M MOPS buffer for pH=7 and pH=8, in 1.2 M MES buffer for pH=6, 6 M HCOONa in all the buffers, $[sub]_r$ = 28 mM, $[cat]_r$ = 0.28 mM. [a] The reactions were carried out for 5 h. [b] Conversion was obtained by HPLC using correction factor of 1.3 for **A**, **B**, **C**, **D** and **E** at λ = 283 nm. Enantiomeric excess was determined using HPLC equipped with chiral OD-H column. For product **B** d.e. >99% (*syn*). [c] the only product results the ethyl 1,2-dihydroisoquinoline-4-carboxylate. [d] See the experimental section for HPLC conditions.

Preliminary studies were first performed to select the best solvent and hydrogen donor. In this regard, buffers revealed the best choice if compared to water whereas *i*PrOH or physiological solution, led to a significant erosion in the reaction conversion (conversion <50% in 24 h in all cases for both CAMPY and Me-CAMPY). In the same way the selection of hydrogen donor proved critical. HCOONa was selected among the others (HCOOH or azeotropic mixture 5:2=TEA:HCOOH) on the base of the achieved enantioselectivity, with a settled ratio of 20:1 to the substrate. In fact, by using a different hydrogen donor, a racemic mixture of the product was obtained in all cases. Conversely, the temperature variation (20°C, 40°C or 60°C) did not show any significant effect on conversion but caused a weak decrease in enantioselectivity (screening data not reported).

The final pH of the solution was screened in a range of 5-8 values, according with the assumption made by Bäckvall that protonated imines can be easily reduced by metal-hydride intermediates enhancing the enantioselectivity of the system.[20] A change in pH did not result in a better enantioselectivity in all cases but in a drop of the reaction rate specially at pH 5 (data not reported). Conversely, the reduction conversion of the precursor of salsolidine **C** remarkably raised up to 99% in only 5 h in the case of the use of CAMPY as ligand at all different pH (Table 2, entries 3-5). As a result of this preliminary screening, the reactions for all the substrate were carried out using $[IrCp^*Cl_2]_2$/CAMPY in MES or MOPS buffer (1.2 M, pH 6-8) in the presence of HCOONa (6 M) at 20°C.

When the ATH reaction was carried out on the most challenging disubstituted isoquinoline **B**, the *syn* diasteroisomers were

obtained with an excellent d.e. (>99%) and an extremely appreciable e.e. in the case of CAMPY (Table 2, entry 10, 72% e.e.) although in a modest conversion (up to 34% e.e.). Most notably, the catalytic system resulted active only at pH 7 whereas acidic conditions proved detrimental for the catalyst performance showing that, in this case, the reduction product was obtained only in traces. The reduction of isoquinolines, aromatic imines, resulted particularly demanding as it has been reported[8a] to take place through the formation of 1,2-dihydroisoquinolines as intermediate. In a presence of a substituent in α position to *N* atom, this enamine is subjected to a rapid enamine-imine tautomerization process affording the 1,4-dihydroisoquinoline that undergoes to a second reduction to the corresponding amine. In the case of substrate **A**, the lack of the substituent in α position might not allow the tautomerization process and the only obtained product resulted the prochiral ethyl 1,2-dihydroisoquinoline-4-carboxylate (Table 2, entries 6-8). Instead regarding the 3,4 dihydroquinoline **D** and **E**, the presence of benzylic substituent in 1 position of the molecules, brought on a decrease in enantioselectivity in comparison to their precursor **C** (Table 2, entries 12-17 *vs* entries 3-5) although the reaction proceeded with better conversion than those obtain with AH reduction process (Table 1, entries 11 and 12). Regarding the ATH of quinaldine **F**, in all cases the reaction rate in 18 h did not allow to obtain complete conversion and the enantioselectivity is comparable to that obtained with the substrate **E** with and e.e. up to 53% (Table 2, entries 18-20 *vs* entries 15-17). For the sulfonyl imines **G**, the ATH confirmed that the reaction rate resulted in very good yield in comparison of AH with a good e.e. obtained at pH 7 (Table 2, entry 22).

Conclusions

The obtained data underlined that for both the reduction methods the reaction rate and the enantioselectivity resulted comparable although with significant differences. The ATH proved to be the method of choice to obtain amines from 3,4 dihydroquinolines, substrates **C**, **D** and **E** and for activated imines as the sulfonyl imine **G**. In fact, ATH reaction gave the best results at pH 7, either for substrate **C** leading to a complete conversion in only 5 h with a good 76% e.e. (Table 2, entry 4) or for **G** allowing to obtain a complete conversion with an appreciable e.e. (Table 1, entry 22, 62% e.e.). On the contrary, AH resulted a valid synthetic tool in the reduction of the most arduous isoquinolines (**A** and **B**) and quinolines (**F**) affording the chiral cyclic amines in quantitative yield for all the substrates with a significant 54% e.e. for a **A**, 51% e.e. for **B** and 64% e.e for **F** when TetraMe-BITIOP was used in iridium cyclooctadiene complex and in the presence of DCDMH (Table 1, entries 3, 6 and 13). In conclusion, ATH resulted a valid alternative to AH only for the reduction of 3,4-dihydroisoquinoline and activated imines. In the case of the most demanding substrates, this approach need further investigation to overcome the limited conversion to the product especially considering the green reaction conditions that this system allowed to apply.

Supporting Information Summary

In Supporting Information are reported Experimental Procedures, NMR- spectra and HPLC spectra.

Keywords: asymmetric reduction • atropoisomeric diphosphines • cyclic imines • iridium complexes

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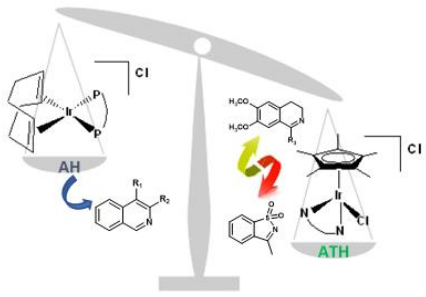
Asymmetric Hydrogenation and Asymmetric Transfer Hydrogenation, based on atropoisomeric diphosphine iridium and chiral diamine iridium complexes respectively, were evaluated in the reduction of quinolines, isoquinolines and 3,4-dihydroisoquinolines. The selection of the appropriate reduction method, is strongly correlated to the electronic and steric properties of the substrate.



Cyclic imines reduction

*G. Facchetti, R. Bucci, M. Fusè, I. Rimoldi**

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Asymmetric Hydrogenation *vs* Transfer Hydrogenation in the Reduction of Cyclic Imines