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Evaluation of Chemical Diversity of Biotinylated Chiral 1,3-Diamines as a Catalytic Moiety in Artificial Imine Reductase

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The possibility of obtaining an efficient artificial imine reductase was investigated by introducing a chiral cofactor into artificial metalloenzymes based on biotin–streptavidin technology. In particular, a chiral biotinylated 1,3-diamine ligand in coordination with iridium(III) complex was developed. Optimized chemogenetic studies afforded positive results in the stereoselective reduction of a cyclic imine, the salsolidine precursor, as a standard substrate with access to both enantiomers. Various factors such as pH, temperature, number of binding sites, and steric hindrance of the catalytic moiety have been proved to affect both efficiency and enantioselectivity, underlining the great flexibility of this system in comparison with the achiral system. Computational studies were also performed to explain how the metal configuration, in the proposed system, might affect the observed stereochemical outcome.

Introduction

Considering that transition-metal complexes and enzymes possess unique and often complementary properties as catalysts, in the last few decades researches have tried to combine the structure and the reactivity of metals and peptides, in a so-called hybrid metal–peptide catalysts[1] for the synthesis of enantiomerically enriched compounds in aqueous media. In more general terms, the development of a hybrid catalyst results from the combination of a biological scaffold (e.g., proteins,[2] DNA,[3] or peptides[4]) with an active catalytic moiety. Among several anchoring strategies exploited to embed chemical complexes within biomolecules (dative, covalent, or supramolecular interactions), the use of biotin–streptavidin technology in forming artificial metalloenzymes has been explored extensively. The success of this approach is related to the ease of self-assembly of these artificial metalloenzymes, which allows for rapid optimization. To improve the performance of hybrid catalysts, the chemogenetic approach was found to be the most suitable strategy.[5] This strategy concerns two distinct optimizations: 1) genetic modification of the protein scaffold, based on computational calculations and X-ray structures; particular attention is given to the active site of enzyme (< 10 Å around the catalytic metal center);[6] 2) chemical fine-tuning of the cofactor to adjust the localization of the catalytic moiety inside the funnel-shaped cavity of the protein.[7]

The Ward group[1j,2a,8] has relied on synthesizing several biotinylated ligands to provide chemical diversity by using achiral five-membered ring chelates. With the aim of studying the robustness of this strategy and to underline a different type of interaction between the protein scaffold and metal catalytic environment, chiral 1,3-diamines were also investigated for the enantioselective reduction of cyclic imines.

Results and Discussion

Based on the biotin–streptavidin technology studied in depth by the Ward group, we synthesized six different biotinylated ligands starting from simple chiral 1,3-diamines, previously reported by our group, which are able to be used as ligands in Ru^{II} complexes for the asymmetric transfer hydrogenation (ATH) of ketones with interesting results regarding the differences in reactivity, especially with respect to different types of reaction media.[9]

Relying on the biotin anchor and the spacer, the catalytic moiety was redesigned by substituting classical 1,2-diamines ligand with enantiopure 1,3-diamine, thus generating a six-membered chelating ring and inserting a bulky substituent at the chiral center. The introduction of these two features could allow us to evaluate the versatility of this supramolecular anchoring approach and see how the change in chiral environment might affect the position of the catalytic moiety within the protein (chiral host), underlining the importance of secondary interactions to achieve selectivity.

The synthesis of the starting amino alcohols was achieved as previously reported.[9] The reaction of *para*-, *meta*-, or *ortho*-nitrobenzenesulfonyl chloride in the presence of triethylamine

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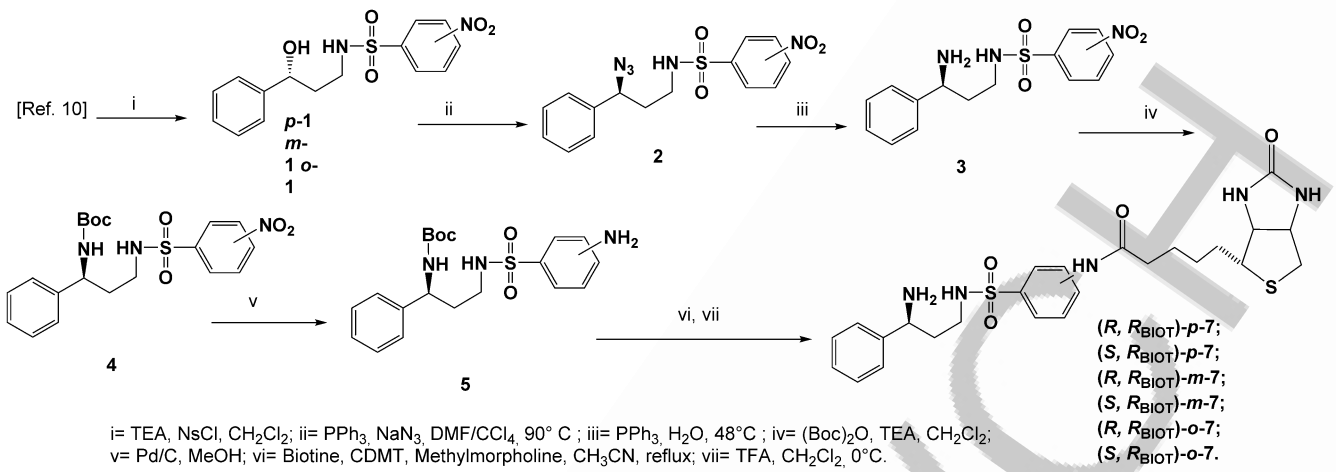


Scheme 1. Synthesis of biotinylated cofactors **7**.

(TEA) produced the corresponding nitrobenzenesulfonamides. Then, the corresponding azido derivatives were achieved after the addition of PPh_3 and NaN_3.[10] In our case, a strong dependence on the solvent did not allow us to directly obtain the corresponding amine in the 3-position. The selective reduction of the azido moiety, without effecting the nitro group, was achieved by using a Staudinger reduction[11] to yield compound **3**. The amino function was protected by employing di-*tert*-butyl dicarbonate and finally the nitro group was reduced by using molecular hydrogen in the presence of Pd/C, thus obtaining compound **5**. A condensation reaction with biotin[12] was performed and the amino function at the chiral center was deprotected by using trifluoroacetic acid (Scheme 1).

The biotinylated ligands were used for the preparation of the corresponding Ir^{III} d^6 piano-stool precatalysts, in quantitative yield, as yellow–orange powders.

The salsolidine precursor was selected as a model substrate (Figure 1). Indeed, given the prevalence of the chiral 1,2,3,4-tetrahydroisoquinoline motif in natural alkaloids and synthetic drugs,[13] the development of methods for its production in enantiopure form is highly desirable.

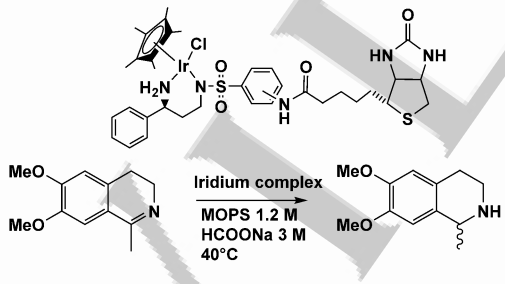


Figure 1. Artificial imine reductases for ATH with chiral 1,3-diamine scaffolds.

A preliminary study with 1,3-diamines as ligands in d^6 Ir piano-stool complexes was realized by using a dihydroisoquinoline analog in aqueous media. Reactions were carried out at 40 °C by using 5 mmol of substrate with 0.5 mol% of iridium complex in 1 mL of MOPS (3-(*N*-morpholino)propanesulfonic acid ■■definition ok?■■) buffer at pH 7 in the presence of HCOONa (3 M) as the hydride source. After 10 h, the conversion was complete but only 5–6% enantioselectivity was achieved. As shown previously for reactions catalyzed by ruthenium(II) complexes,[9] the conformational freedom of the chelating six-membered ring might negatively affect enantioselectivity. However, by inserting a bulky substituent at the 3-position and introducing these complexes in a rigid supramolecular system (Sav/biotinylated metal complex), we expect to increase the energy barrier for conformational change.

Nevertheless, considering that the reduction of these substrates is often not easy to obtain, our preliminary results in terms of reaction conversion could be considered a good starting point to study the development of artificial imine reductases by using these chiral 1,3-diamines as ligands in transition-metal complexes.[14]

In this study, streptavidin WT and mutant S112X were selected for screening. Indeed, previous computational studies and the crystal structure of Sav/biotinylated iridium(III) hybrid complexes, in which the ligand was achiral ethylenediamine,[8a,12] indicated residue 112 as one of the most critical in determining the final stereochemical outcome.

As an initial screening, we investigated the catalytic activity of the d^6 Ir^{III} piano-stool bearing biotinylated aminosulfonamide ligands (**7**) as bare catalysts and their combination with wild-type streptavidin (Sav WT, hereafter) for the production of salsolidine, taking account of different reaction parameters such as pH, temperature, substrate concentration, and catalyst loading (Table 1).

The results, displayed in Table 1, illustrate the very high activity of the iridium piano-stool biotinylated aminosulfonamide catalysts. In all cases, however, modest stereoselectivity occurred. A similar behavior was observed for all diverse chemical entities (*para*, *meta*, or *ortho* derivatives), suggesting the inefficacy of the chiral center on a flexible six-membered chelating ring. Conversely, when the transition-metal catalyst is embedded in Sav WT, a slight decrease in activity was observed (Table 1, entries 2, 4, 8, 10, and 12). An improvement of stereo-

Table 1. Optimized screening with or without Sav WT.[a]

Entry	Protein	Complex	pH	*T* [°C]	Conversion [%]	*ee* (config)[b] [%]
1	–	[Cp*Ir(Biot-*p*-(*R*)-**7**)Cl]	7.0	40	>99	6 (*S*)
2	Sav WT[c]	[Cp*Ir(Biot-*p*-(*R*)-**7**)Cl]	7.0	40	58	5 (*R*)
3	–	[Cp*Ir(Biot-*p*-(*S*)-**7**)Cl]	6.5	30	>99	5 (*R*)
4	Sav WT[c]	[Cp*Ir(Biot-*p*-(*S*)-**7**)Cl]	6.5	30	83	18 (*R*)
5	–	[Cp*Ir(Biot-*m*-(*R*)-**7**)Cl]	7.0	40	>99	4 (*S*)
6	Sav WT[c]	[Cp*Ir(Biot-*m*-(*R*)-**7**)Cl]	7.0	40	>99	5 (*R*)
7	–	[Cp*Ir(Biot-*m*-(*S*)-**7**)Cl]	6.5	30	>99	–
8	Sav WT[d]	[Cp*Ir(Biot-*m*-(*S*)-**7**)Cl]	6.5	30	76	8 (*R*)
9	–	[Cp*Ir(Biot-*o*-(*R*)-**7**)Cl]	7.0	40	>99	–
10	Sav WT[c]	[Cp*Ir(Biot-*o*-(*R*)-**7**)Cl]	7.0	40	90	–
11	–	[Cp*Ir(Biot-*o*-(*S*)-**7**)Cl]	6.5	30	>99	–
12	Sav WT[d]	[Cp*Ir(Biot-*o*-(*S*)-**7**)Cl]	6.5	30	72	–

[a] All reactions were carried out for 24 h by using 1 mol% complex **7** and with or without 0.33 mol% tetrameric Sav WT in 1.2 M MOPS buffer, with 3 M HCOONa [b] Conversion was obtained by HPLC by using a correction factor of 1.32 at $\lambda = 283$ nm. Enantiomeric excess was determined by using HPLC equipped with a chiral OD-H column. Eluent: hexane/EtOH = 95:5, 0.1% diethanolamine (DEA), flow = 0.8 mL min^{-1}. [c] $[sub]_f$ = 28 mM, $[cat]_f$ = 0.28 mM. [d] $[sub]_f$ = 35 mM, $[cat]_f$ = 0.35 mM.

Table 2. Optimized screening with S112X and [Cp*Ir(Biot-**7**)Cl].

Entry	Protein	Complex	pH	*T* [°C]	Conversion [%]	*ee* (config) [%]
1	S112K	[Cp*Ir(Biot-*p*-(*R*)-**7**)Cl]	7.0	40	47[a]	12 (*S*)
2	S112R	[Cp*Ir(Biot-*p*-(*R*)-**7**)Cl]	7.0	40	43[a]	12 (*S*)
3	S112C	[Cp*Ir(Biot-*p*-(*S*)-**7**)Cl]	6.5	30	40[b]	58 (*R*)
4	S112C	[Cp*Ir(Biot-*p*-(*S*)-**7**)Cl]	6.5	30	60[c]	65 (*R*)
5	S112Y	[Cp*Ir(Biot-*m*-(*R*)-**7**)Cl]	7.0	40	72[c]	47 (*S*)
6	S112Y	[Cp*Ir(Biot-*m*-(*R*)-**7**)Cl]	7.0	40	72[c,d]	37 (*S*)
7	S112C	[Cp*Ir(Biot-*m*-(*S*)-**7**)Cl]	6.5	30	26[b]	40 (*R*)
8	S112E	[Cp*Ir(Biot-*m*-(*S*)-**7**)Cl]	6.5	30	79[b]	12 (*R*)
9	S112M	[Cp*Ir(Biot-*o*-(*R*)-**7**)Cl]	7.0	40	95[a]	9 (*R*)
10	S112Q	[Cp*Ir(Biot-*o*-(*S*)-**7**)Cl]	6.5	30	78[b]	19 (*R*)
11	S112E	[Cp*Ir(Biot-*o*-(*S*)-**7**)Cl]	6.5	30	73[b]	18 (*R*)

[a] Reactions were carried out at 40 °C for 24 h by using 1 mol% complex **7** with or without 0.33 mol% tetrameric WT or mutant Sav in 1.2 M MOPS buffer, 3 M HCOONa, pH 7.0, $[sub]_f$ = 28 mM, $[cat]_f$ = 0.28 mM. [b] Reactions were carried out at 30 °C for 48 h by using 1 mol% complex **7** and 0.33 mol% tetrameric WT or mutant Sav in 1.2 M MOPS buffer, 3 M HCOONa, pH 6.5, $[sub]_f$ = 35 mM, $[cat]_f$ = 0.35 mM. [c] 1 mol% complex **7** and 0.66 mol% tetrameric mutant Sav. [d] $[sub]_f$ = 35 mM, $[cat]_f$ = 0.35 mM.

selectivity, always leading to a reaction product in the (*R*)-configuration, was obtained with the *para* iridium catalyst (Table 1, entry 4, 18% *ee*). For [Cp*Ir(Biot-*m*-(*R*)-**7**)Cl] and [Cp*Ir(Biot-*p*-(*R*)-**7**)Cl] (Cp* = pentamethylcyclopentadienyl) in the presence of Sav WT, comparing the bare catalyst and the hybrid catalyst, a modest inversion of product configuration was highlighted (Table 1, entry 1 versus 2 and entry 5 versus 6).

A genetic optimization of the Sav host protein was then performed and different mutants at position 112 were tested (see the table in the Supporting Information).

Selected results for the chemical and the genetic optimization in the presence of [Cp*Ir(Biot-**7**)Cl] are summarized in Table 2.

To provide a rationale behind the activity of the catalysts reported here, a computational study was performed by evaluating two different mutants, namely S112C and S112Y, at position 112 (Table 2, entries 4 and 5).[8b] Indeed, this position is close to the biotinylated metal when incorporated into streptavidin in the presence of the achiral 1,2-diamine used as the ligand. Models were generated starting from the tetrameric biological assembly of the X-ray crystal structure reported in the literature (PDB: 3K2).[8a] Only monomers A and C were considered to build a dimer with a fully functional binding site for one biotinylated ligand. The Ser residue at position 112 was then mutated to Cys or to Tyr and the sidechain positioning was evaluated by a systematic conformational search using the MOE software (see the Supporting Information for further computational details).[15] The original ethylenediamine ligand was then modified to obtain [Cp*Ir(Biot-*p*-(*S*)-**7**)Cl]⊂Sav S112C and [Cp*Ir(Biot-*m*-(*R*)-**7**)Cl]⊂Sav S112Y. Finally, the chloride was substituted with a hydride to mimic the active catalyst, thus causing an inversion of configuration at the metal center according to the Cahn–Ingold–Prelog rule.[16] For each complex, both pseudoenantiomers at the metal center (hereafter indicated as R_{Ir} and S_{Ir}) were generated with the aim to clarify how the metal configuration in the [Cp*Ir(Biot-*p*-(*S*)-**7**)H]⊂Sav S112C and [Cp*Ir(Biot-*m*-(*R*)-**7**)H]⊂Sav S112Y (hereafter abbreviated as *p*-S112C and *m*-S112Y, respectively) might affect the reaction stereoselection.

By visually inspecting the (R_{Ir})- and (S_{Ir})-*p*-S112C models (Figure 2), it was immediately evident that only the former

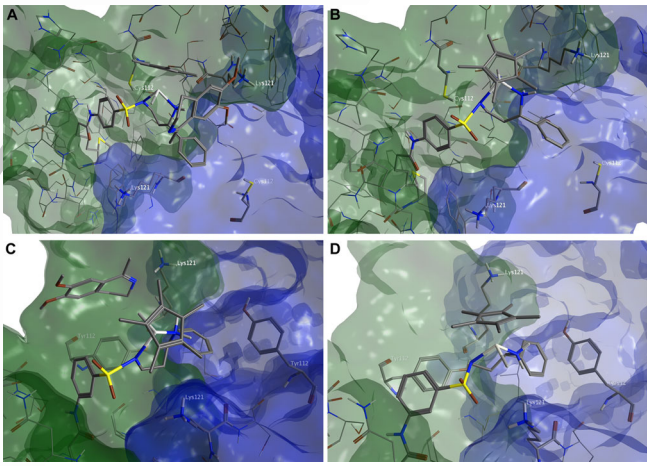


Figure 2. Computational models of A) (R_{Ir})-[Cp*Ir(Biot-*p*-(*S*)-**7**)H]⊂Sav S112C complex bound to the favored pro-*R* configuration of salsolidine precursor; B) unbound (S_{Ir})-[Cp*Ir(Biot-*p*-(*S*)-**7**)H]⊂Sav S112C complex; C) (S_{Ir})-[Cp*Ir(Biot-*m*-(*R*)-**7**)H]⊂Sav S112Y complex bound to the favored pro-*S* configuration of the salsolidine precursor; D) unbound (R_{Ir})-[Cp*Ir(Biot-*m*-(*R*)-**7**)H]⊂Sav S112Y. For all models, chains A and C are represented as green or blue molecular surfaces, respectively.

structure is suitable for the hydride transfer. Indeed, with the metal center in the R_{Ir} configuration the reactive center is exposed outside of the biotinylated ligand binding site (Figure 2 A). Conversely, when the metal adopts the S_{Ir} configuration, the cyclopentadienyl moiety is solvent-exposed and the

reactive hydride atom is completely hindered by the protein loop spanned by residues 112–122 (Figure 2B).

Similarly, when considering the (S_{Ir})- and (R_{Ir})-*m*-S112Y models, it can be observed that in the former complex the hydride atom can be easily accessed by the salsolidine precursor (Figure 2C), whereas in the latter, the reaction center is hindered by the sidechain of Lys121 in protein chain C (Figure 2D).

Finally, we also evaluated the potential binding mode of the cyclic imine 1-methyl-6,7-dimethoxy-3,4-dihydroquinoline, which was used as a standard substrate (see the Supporting Information). The precursor was manually docked in the (R_{Ir})-*p*-S112C and (S_{Ir})-*m*-S112Y models, according to the indication reported in ref. [17], evaluating several possible substrate orientations in both the pro-*R* and pro-*S* configurations. Concerning the (R_{Ir})-*p*-S112C complex, the docked pro-*R* configuration (Figure 2A) was favored over the pro-*S* configuration (Figure S1A, in the Supporting Information) by 0.9 kcal mol^{-1}, in agreement with experiments, even if this result should be treated with caution as the energy difference is beyond the accuracy limit of the method. In both cases, the substrate is stabilized by hydrogen-bonds between the two methoxy groups and the NH_3^+ group of Lys121 (2.40 and 2.00 Å for the pro-*R*, and 2.63 and 2.01 Å for the pro-*S* configuration). Moreover, it was also observed that the H···C=N distance in the pro-*R* configuration was 1.14 Å shorter than that in the pro-*S* (Table S4, in the Supporting Information).

Conversely, when considering the (S_{Ir})-*m*-S112Y model as the receptor, a lower docking energy was obtained for the pro-*S* configuration. By inspecting the geometry of the two complexes, a shorter H···C=N distance was found for the pro-*S*, whereas in both complexes we observed the possibility for Lys121 to act as an acidic catalysis trough a hydrogen-bond between the NH_3^+ group of Lys121 and the dihydroquinoline nitrogen (1.82 and 1.87 Å for the pro-*S* and pro-*R* configurations, respectively; Figure 2C and Figure S1B, in the Supporting Information).

Finally, compared with WT Sav, both S112C and S112Y mutations concur in creating a hydrophobic pocket, in chain C, which accommodates well the phenyl moiety on the six-membered ring (Figure 2). Thus, in both the *meta* or *para* substitution patterns, the ring is forced into a single conformation, with an equatorial orientation of the phenyl group, and consequently its flexibility is reduced.

From the experimental results and from the computational study, different trends emerged:

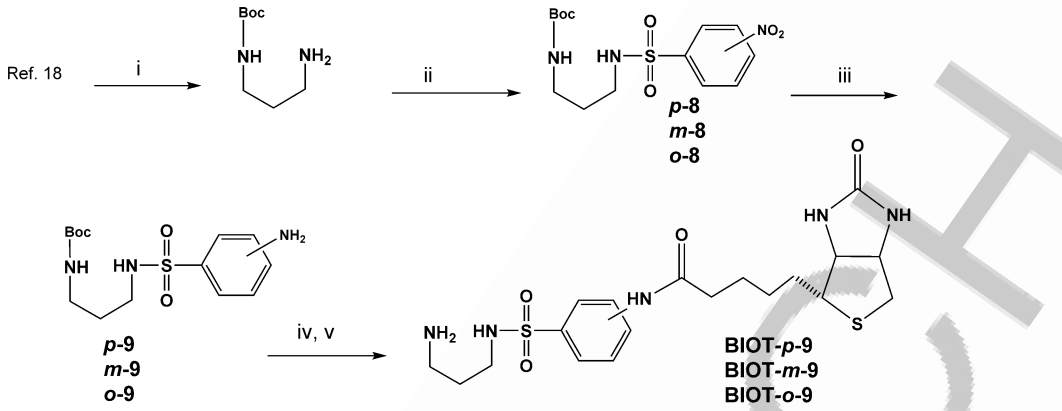
1) In all cases, incorporation of biotinylated metal complexes within mutant Sav S112X leads to decreased conversion.
2) The optimal pH was 6.50 for [Cp*Ir(Biot-(*S*)-**7**)Cl]⊂Sav S112X and pH 7.0 for [Cp*Ir(Biot-(**R**)-**7**)Cl]⊂Sav S112X; changes in temperature were not as significant, even if the best results were obtained at 30 °C and 40 °C, respectively.
3) Streptavidin is a homo-tetramer protein but only three biotin binding sites were determined by using an assay with biotin-4-fluorescein;[17] nevertheless, different [Cp*Ir(-Biot-**7**)Cl]/Sav S112X ratios confirmed that 1:2 (versus biotin binding sites) yields the best results (entries 3 versus 4 and entry 5).
4) When [Cp*Ir(Biot-(*R*)-**7**)Cl] was incorporated into Sav mutants, the preferred chemical diversity was the *meta* position of the linker; conversely, the iridium precatalyst bearing the *S* diamine matched better with Sav when the *para* position of this one was realized. These data confirm the role of the bulky phenyl group on the stereocenter in influencing the ability of the iridium biotinylated catalyst to be deeply anchored into the biotin-binding cavity in accordance with our computational findings and "induced lock-and-key hypothesis".[16]
5) The best results in terms of enantioselectivity were obtained with [Cp*Ir(Biot-*p*-(*S*)-**7**)Cl]⊂Sav S112C (entry 4, 66% (*R*) *ee* and 60% yield) and with [Cp*Ir(Biot-*m*-(*R*)-**7**)Cl]⊂S112Y (entry 5, 47% (*S*) *ee* and 72% yield). A rationale for this finding was provided by our computational study.
6) Generally, the stereoselection in favor of the *S* enantiomer product was accomplished with a lower *ee*, just like in the results obtained with ethylenediamine as ligand.[8a] The unfulfilled enantioselectivity in these cases was probably due to the preference for the *R* enantiomer as evident in all cases with the Sav WT system (Table 1 versus Table 2).
7) When diamine ligands were in the *R* configuration, the reduction product salsolidine was obtained in the *S* configuration; an exception was with the [Cp*Ir(Biot-*o*-(*R*)-**7**)Cl] catalyst, which afforded the product in *R* configuration albeit in a very modest 9% *ee* (entry 9). This last catalyst was revealed as the worst of the series (see the Supporting Information). Conversely, the *S* configuration of diamines led to the *R* enantiomer of salsolidine. As in the previous biotin–streptavidin technology system, this behavior was strictly related to the enantiodiscrimination generated by the protein at the racemic iridium center; therefore, the enantioselective reduction of the considered substrate seems to rely on the chirality at the metal center. The nearby bulky phenyl residues appear to be important in modulating protein–catalyst interactions. However, they do not seem to be relevant in determining the stereoselectivity by guiding the approach of the substrate to the catalyst.

With the aim of clarifying and confirming our assertions about the behavior of the here-reported chiral 1,3 biotinylated diamine ligands, the synthesis of achiral 1,3-ligands and tests of the catalytic performances of their Ir(Cp) complexes were performed.

The synthesis proceeded starting from 1,3-diaminopropane,[18] as shown in Scheme 2, mirroring the synthesis of the chiral ligands.

The resulting achiral *o*-, *m*-, and *p*-biotinylated diamines were used for preparing the corresponding iridium(III) complexes, then used in ATH of the salsolidine precursor under the same reaction conditions as were used for the chiral ligands. The results are reported in the Supporting Information (see Table S2) and the optimized data are summarized in Table 3.

When the achiral system containing ligands **10** was used, the product was mainly obtained in the *R* configuration, with



i= $(Boc)_2O$, dioxane, rt; ii= TEA, NsCl, CH_2Cl_2; iii= Pd/C, Ethylacetate, 20 atm, 4 h; iv= Biotine, CDMT, Methylmorpholine, CH_3CN, reflux; v= TFA, CH_2Cl_2, 0°C.

Scheme 2. Synthesis of biotinylated cofactors **10**.

Table 3. Optimized screening with S112X and [Cp*Ir(Biot-**10**)Cl].

Entry	Protein	Complex	pH	*T* [°C]	Conversion [%]	*ee* (*R* config) [%]
1	S112C	[Cp*Ir(Biot-*p*-**10**)Cl]	7.0	40	25	83
2	S112C	[Cp*Ir(Biot-*m*-**10**)Cl]	7.0	40	15	52
3	S112C	[Cp*Ir(Biot-*o*-**10**)Cl]	7.0	40	15	56

All reactions were carried out at 40 °C for 48 h by using 1 mol% complex **10** with or without 0.33 mol% tetrameric WT or mutant Sav ($[protein]_f$ = 0.28 mM) in 1.2 M MOPS buffer, 3 M HCOONa, pH 7.0, $[sub]_f$ = 10 mM, $[cat]_f$ = 0.14 mM.

good *ee*, only in the presence of the S112C mutant. The increased enantiodifferentiation ability shown by the achiral ligand might be due to the presence of the chiral pocket close to the reactive iridium catalytic site. In this case, in fact, the lack of an additional bulky group weakly affects both the binding of the substrate with the catalytic complex and the interaction of the biotinylated catalysts at the interface of chain A and C (Figure 2A, B). Conversely, in the presence of mutant S112Y, the phenyl ring at position 1 might increase the stabilization of the complex by interacting with Y112 in chain C (Figure 2C, D), with a positive effect on both yield and *ee*, in this case for the *S* enantiomer. Thus, the presence of a bulky chiral center, as in diamines **7**, especially with *meta* chemical diversity, offers the chance of modulating the stereoselectivity at the metal, allowing the preparation of the *S* enantiomer also, although with moderate enantioselectivity.

Conclusions

The combination of chelating six-membered-ring transition-metal complexes containing *para* biotinylated aminosulfonamide with Sav S112C in the formation of imino reductases was able to reduce cyclic 1-methyl-6,7-dimethoxy-3,4-dihydroquinoline, a precursor of salsolidine, with 66% *ee* for the *R* product under ATH conditions when the chiral diamine moiety was in the *S* configuration, although the best result was obtained by using the homologue achiral ligand with a 83% *ee*. In regard to the formation of *S*-salsolidine, the *meta* diversity of the linker position at the stereocenter in the *R* configuration of the ligand allowed us to obtain 47% *ee* with the Sav S112Y mutant. Although the chiral d^6 Ir^{III} piano-stool biotinylated complexes worked in the reduction of cyclic amine with very low enantioselectivity, the presence of the biological scaffold allowed us to introduce a new source of chirality with good activity and enantioselectivity depending, as confirmed by computational studies, on the enantiodiscrimination at the metal center operated by the protein. In other words, although the bare catalysts or their associated he complexes within Sav WT revealed a lack of enantiodiscrimination, the combination of chemical and genetic optimization showed a synergistic effect in terms of enantioselectivity in both the achiral system and in the chiral one.

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Keywords: asymmetric transfer hydrogenation · chiral diamines · imino reductase · metalloenzymes · salsolidine

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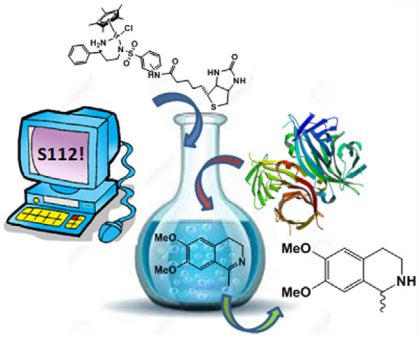

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Evaluation of Chemical Diversity of Biotinylated Chiral 1,3-Diamines as a Catalytic Moiety in Artificial Imine Reductase

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