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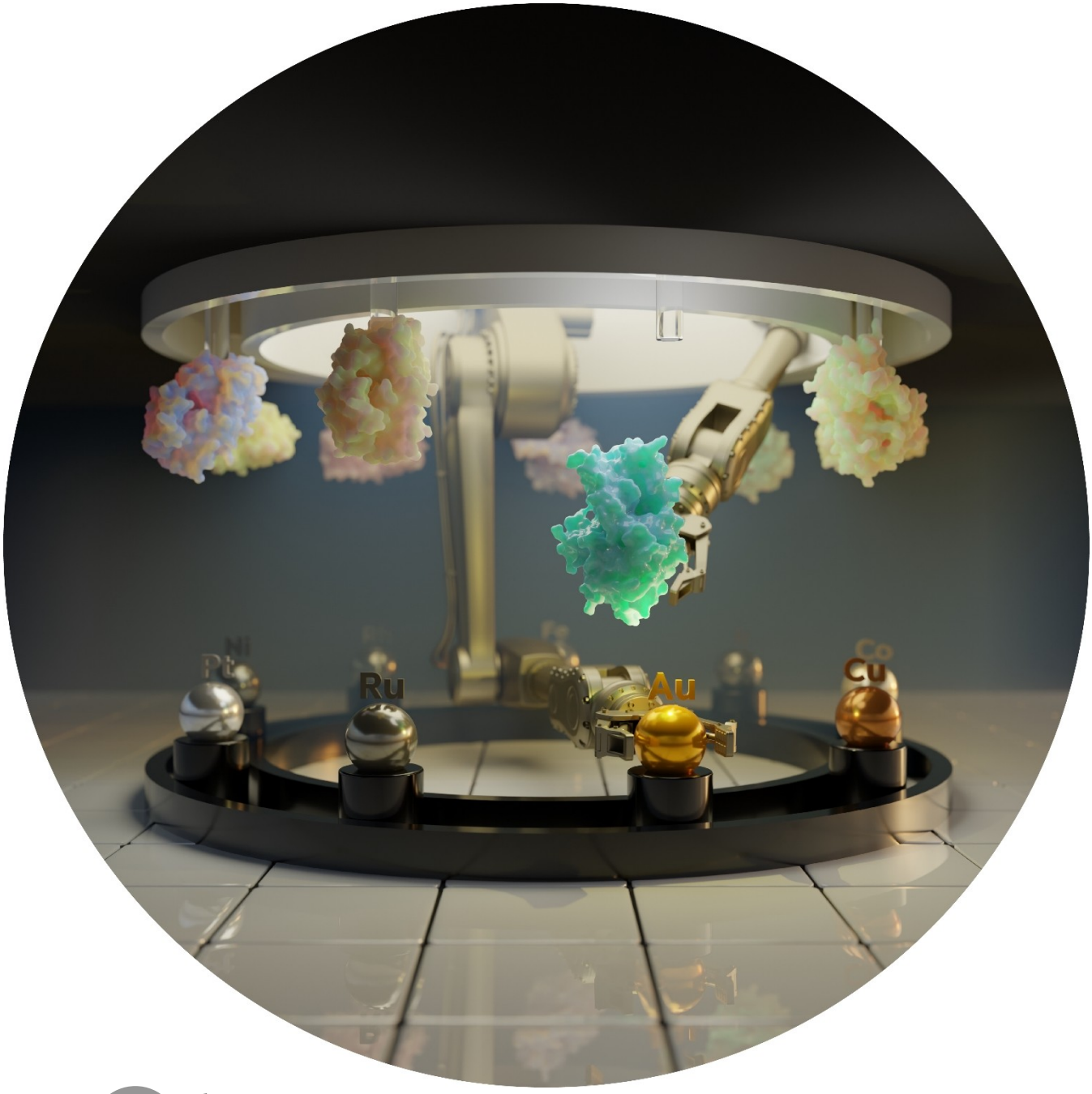
Biocatalysis

Chemoenzymatic Cascades Combining Biocatalysis and Transition Metal Catalysis for Asymmetric Synthesis

Sergio González-Granda, Lorena Escot, Iván Lavandera, and Vicente Gotor-Fernández**



Abstract: The combination of catalytic methods provides multiple advantages in organic synthesis, allowing access to diverse organic molecules in a straightforward manner. Merging metal and enzyme catalysis is currently receiving great attention due to the possibility to assemble metal catalysis in C–C coupling, olefin metathesis, hydration and other reactions with the exquisite stereospecificity displayed by enzymes. Thus, this minireview is organized based on the action of the metal species (Pd, Ru, Au, Ir, Fe…) in combination with different enzymes. Special attention will be paid to the design of sequential processes and concurrent cascades, presenting solutions such as the use of surfactants or compartmentalization strategies for those cases where incompatibilities could hamper the overall process.

1. Introduction

Enzyme catalysis is nowadays considered a powerful tool for synthetic chemists, providing stereoselective access towards broad families of compounds.[1] Advances in immobilization, molecular biology and bioinformatic studies have paved the way to perform biotransformations in different media, improving the biocatalyst stability and activity, discovering new enzymatic pathways and rationalizing mechanistic considerations.[2] All these achievements have enabled efficient individual reactions, finding even more advantages when assembling several steps in a unique reaction vessel. In this context, the design of multienzymatic transformations in one-pot has simplified linear complex routes, avoiding the isolation of unstable intermediates to obtain the final products in higher yields. At the same time, the combination of several enzymes made possible the development of orthogonal, parallel and cyclic cascades, shifting the reaction equilibrium or favoring the formation of a desired compound.[3]

The potential of enzymes has gained more attention since their combination with other types of catalysts is possible, highlighting recent achievements in their cooperative action with metal species,[4] organocatalysts[5] and/or under light irradiation conditions.[6] Traditionally, the use of metals and enzymes was exclusively devoted to dynamic kinetic resolutions (DKRs) of racemic alcohols and amines. The combination of lipases such as *Candida antarctica* lipase type B (CAL-B) and *Pseudomonas cepacia* lipase (PSL) with Fe, Pd, Ru and V species, provides straightforward access to enantiopure products in theoretically 100 % yield.[7] Interestingly, these chemoenzymatic processes can be developed in a concurrent mode and under harsh conditions for the metal activation and racemization reaction, due to the thermostability of the immobilized hydrolases. Probably, this is the starting point that has motivated many research groups to explore the combination of metal and enzyme catalysts, appearing striking stereoselective transformations that have been here reviewed and highlighted.

This minireview has been classified depending on the metal-catalyzed reaction, and efforts have been paid to identify key items to address the compatibility between the enzyme and the metal species. Thus, the selection of sequential or concurrent processes will be fundamental to explore the possible inactivation suffered by one or both catalysts due to the presence of some reactants. Methods to overcome these limitations will also be presented, which includes the use of surfactants or compartmentalization strategies, among others.

2. Metal-Enzyme Cascade Processes

Metal-enzymatic concurrent cascades and sequential transformations will be disclosed, focusing first on the role of Pd, Ru, Au, Ir, and Fe species to catalyze multiple organic transformations (C–C couplings, isomerizations, hydrations…), to later consider other metallic species (Cu, Ni, Rh, Pt, and Co) whose combination with enzymes is still in its infancy. Gladly, the overall chemoenzymatic processes will allow the production of chiral products due to the action of stereospecific enzymes including alcohol oxidases, aldolases, alcohol dehydrogenases, amine dehydrogenases, amino acid dehydrogenases, amine transaminases, arylmalonate decarboxylases, ene-reductases, imine reductases, nitrile hydratases or phenylalanine ammonia lyases, among others.

2.1. Palladium (Pd)

Pd chemistry has allowed the development of a huge number of transformations, including the synthesis of complex natural products and drugs.[8] Although, Pd species have been traditionally used as racemization agents in DKRs,[7,9] other Pd-enzyme applications have appeared, which are reviewed below.

2.1.1. Suzuki Coupling

Since its discovery, cross-coupling reactions are the most useful approaches to construct new carbon–carbon or carbon–heteroatom bonds. The great importance of this reactivity was demonstrated by the awarding of the Nobel prize to Prof. Heck, Negishi, and Suzuki in 2010.[10] Its synthetic potential has not gone unnoticed by the biocatal-

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ysis community, so the merging of coupling reactions with biocatalytic steps has been explored to achieve multicatalytic asymmetric transformations. Usually, incompatibilities have been found between both steps such as cross-inhibitions due to the presence of cofactors, reactants or intermediates, or the preference for different solvents or temperatures, so these protocols must be accomplished in a sequential manner.[3c]

Suzuki reaction is the most popular cross-coupling reaction, the low toxicity of boron species enabling the construction of complex molecules including a large number of pharmaceuticals.[11] Gröger and co-workers described a seminal work in this field,[12] consisting of the sequential Suzuki coupling and asymmetric bioreduction catalyzed by an alcohol dehydrogenase (ADH). Hence, the organometallic step was carried out in water using $Pd(PPh_3)_2Cl_2$ and different boronic acids at 70 °C. After finishing this step, ADH from *Rhodococcus* sp., 2-propanol (2-PrOH) and reduced nicotinamide adenine nucleotide cofactor (NADH) were added at room temperature, obtaining 3 enantiopure biaryl alcohols (67–91 % conv., Scheme 1A). Similarly, the synthesis of chiral drug intermediates such as an Odanacatib precursor was accomplished by a Pd-catalyzed Suzuki coupling and bioreduction sequence using *Ralstonia* sp. ADH (*Ras*ADH) (Scheme 1B).[13]

Deep eutectic solvents (DES)[14] mixed with aqueous systems have allowed the design of several metal-enzyme combinations in a sustainable manner. For instance, the Suzuki-coupling of 4′-haloacetophenones with arylboronic acids was reported at 70–100 °C in a choline chloride-glycerol-buffer mixture followed by the bioreduction of the ketone intermediates at 30 °C.[15]

Suzuki cross-coupling reaction has also been combined with ene-reductases (EREDs) for the stereoselective reduction of C–C double bonds. Jiang and co-workers described the reaction between 2-iodocycloenones and boronic acids employing an immobilized Pd catalyst in dendritic organosilica nanoparticles (DON@Pd), followed by asymmetric alkene reduction using the YqjM ERED from *Bacillus subtilis* (Scheme 2).[16] Thus, chiral α-aryl cyclic ketones were successfully obtained (40–81 % yield and 91 to >99 % *ee*). Remarkably, an additional asymmetric reduction step was developed in one-pot, using ADH-A from *Rhodococcus ruber* for the synthesis of (1*S*,2*R*)-2-phenylcyclohexan-1-ol.

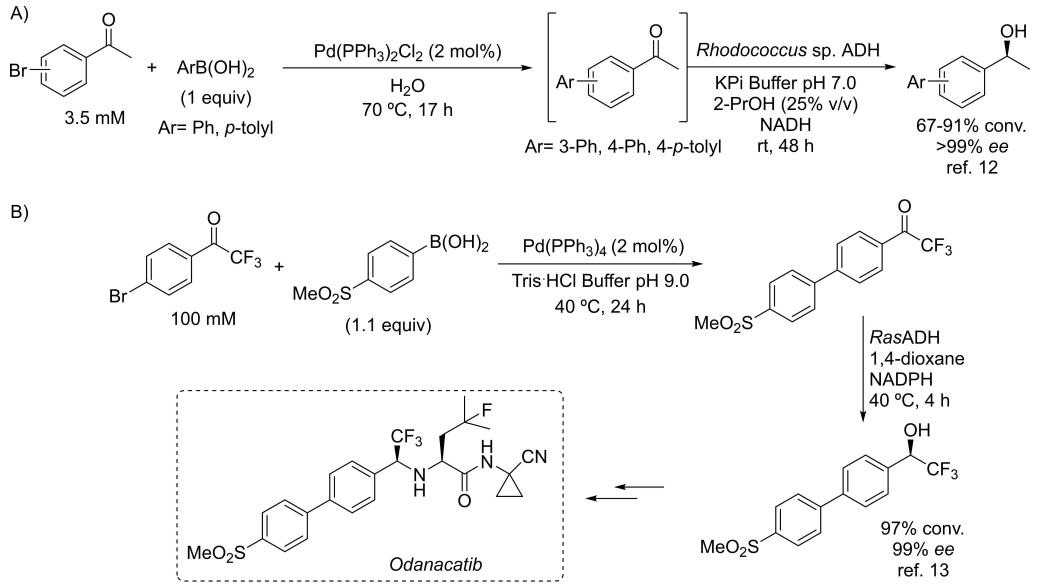
The combination of Pd-catalyzed Suzuki-couplings and enzymatic synthesis of chiral amines has also been described using a series of enzymes such as D-amino acid dehydrogenases (DAADHs), phenylalanine ammonia lyases (PALs) and amine transaminases (ATAs). For instance, Turner and co-workers described the reductive amination of 4-bromophenylpyruvic acid using an engineered DAADH from *Corynebacterium glutamicum* to produce the corresponding D-amino acids (Scheme 3A),[17] which was subjected to N-protection and subsequent Suzuki cross-coupling with aryl boronic acids and $PdCl_2(CH_3CN)_2$ (10 mol %) under microwave conditions. These steps were developed in a one-pot sequential fashion, recovering enantiopure D-biaryl amino acids in 40–70 % yield. Alternatively, the synthesis of the L-derivatives was described through asymmetric hydroamination reaction of 4-bromocinnamic acid with an engineered PAL from *Anabaena variabilis* (AvPAL-F107A), which after isolation and one-pot N-protection and Suzuki-coupling, provided the L-biaryl amino acids in 33–65 % yield (Scheme 3A).

Dr. Sergio González-Granda (1993) studied chemistry at the University of Oviedo where he graduated in 2017, recently completing his Ph.D. studies under the supervision of Prof. I. Lavandera and Prof. V. Gotor-Fernández working in the design of concurrent cascades combining gold(I) species and enzymes. His main research interests include the combination of biocatalysis with other methodologies such as metal- or photocatalysis to develop new synthetic routes and activation modes.

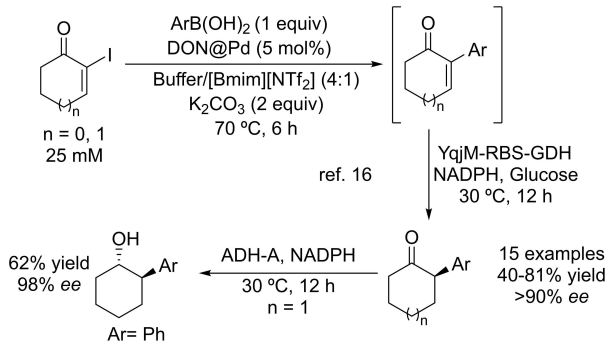
Lorena Escot (1996) studied chemistry at the University of Almería where she graduated in 2020. Then, she moved to Oviedo starting her master studies and later the Doctoral Thesis under the supervision of Prof. I. Lavandera and Prof. V. Gotor-Fernández. Her main research interests include the use of different biocatalysts such as alcohol dehydrogenases, amine transaminases and ene-reductases, and their combination with metal-catalyzed transformations, paying special attention to gold catalysis.

Dr. Iván Lavandera completed his Ph.D. studies in 2003 at the University of Oviedo, and since 2015 is Associate Professor at its Organic and Inorganic Chemistry Department. He is co-author of more than 110 publications, including the edition of the book "Biocatalysis for Practitioners" in 2021. His main research interests are focused on biocatalysis, especially the use of oxidoreductases and transferases to develop green processes, and also new synthetic routes combining bio- and chemocatalysis in a concurrent manner.

Dr. Vicente Gotor-Fernández completed his Ph.D. studies in 2001 at the University of Oviedo, and since 2012 is Associate Professor at its Organic and Inorganic Chemistry Department. He is currently co-author of around 170 publications in the fields of biocatalysis and organic synthesis. His main research interests are focused on the development of multicatalytic processes involving the use of enzymes.



Scheme 1. Examples of Suzuki-ADH sequential approaches to synthesize enantioenriched biaryl alcohols.

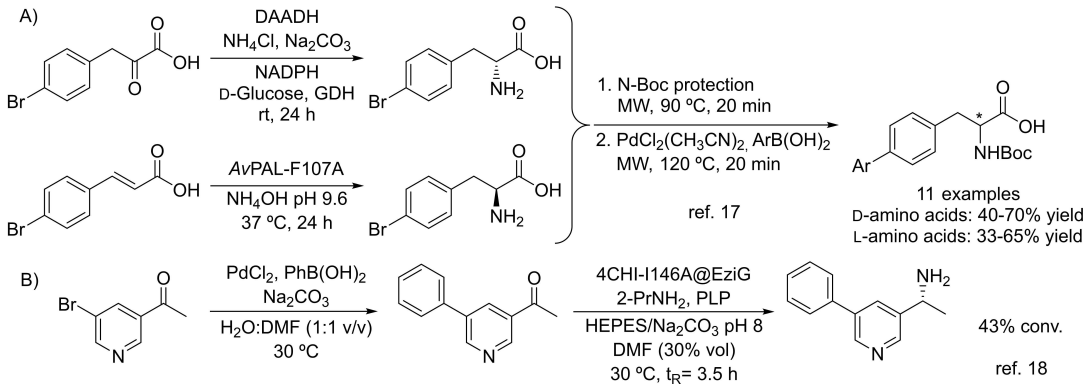


Scheme 2. Merging Suzuki coupling and ERED to obtain chiral cyclic ketones, including a later carbonyl reduction to create an additional stereogenic center.

Bornscheuer and co-workers have described a Pd-catalyzed Suzuki coupling and ketone bioamination using evolved ATA from *Aspergillus fumigatus* (4-CHI-I146A), to obtain chiral biaryl amines.[18] $PdCl_2$ was found as the ideal catalyst for the first step, achieving the synthesis in flow mode of 1-(5-phenylpyridin-3-yl)ethanamine (43 % conv.) by choosing a metal-affinity resin for ATA immobilization (Scheme 3B). The synthesis of other chiral biaryl amines has also been described using DES-buffer mixtures developing the Pd-catalyzed coupling at a remarkable 200 mM substrate concentration, and diluting the reaction mixture to 25 mM for the bioamination, using in this case a TA from *Exophiala xenobiotica.*[19]

2.1.2. Wacker-Tsuji Oxidation

Wacker-Tsuji oxidation allows the synthesis of carbonyl compounds from alkenes using Pd species as catalysts, and generally Cu species as co-oxidants under aerobic conditions.[20] In recent years, its combination with stereoselective biotransformations has been exploited to demonstrate the versatility of styrenes and allyl(hetero)arenes in organic synthesis.[21–23] Undoubtedly, Gröger's group has



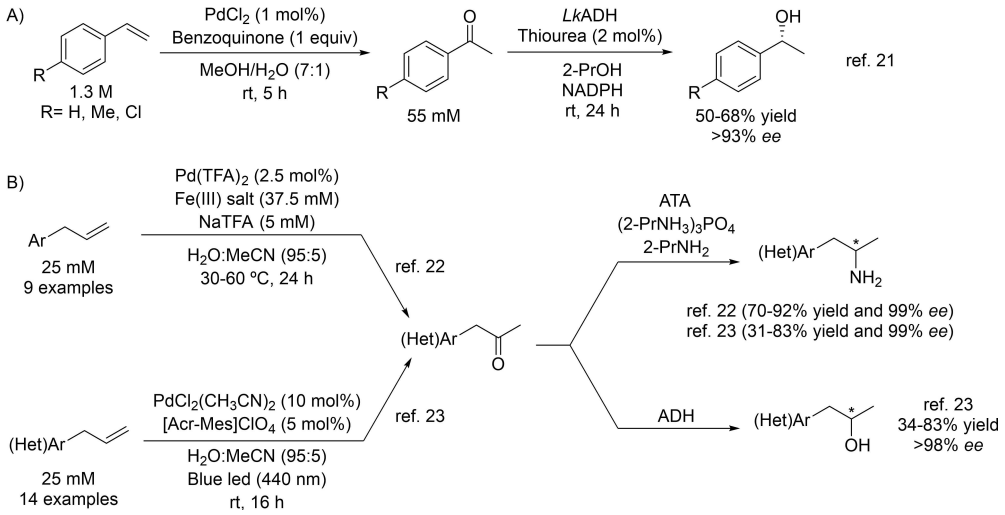
Scheme 3. Combination of Pd-catalyzed Suzuki coupling and enzymatic chiral amino acid and amine syntheses.

largely contributed to the development of this field, and a pioneer work was published in 2012 focusing on a Wacker-Tsuji oxidation and bioreduction sequence to obtain chiral 1-arylethan-1-ols.[21] The oxidation step was performed in MeOH:water (7:1 v/v) to transform styrenes into 1-arylethanones using $PdCl_2$ as catalyst and benzoquinone as co-oxidant, while the bioreduction was sequentially developed adding *Lactobacillus kefir* ADH (*Lk*ADH), NADPH and 2-PrOH to the reaction medium. The conversion of the one-pot approach was very low due to the enzyme inhibition suffered by the Pd species generated in the oxidation step. To overcome this drawback, a catalytic amount of thiourea was added. After optimization, three 1-arylethanols were synthesized (50–68 % yield, >93 % *ee*, Scheme 4A). Further improvements were later achieved by the same research group using a compartmentalization strategy that will be discussed in Section 3.

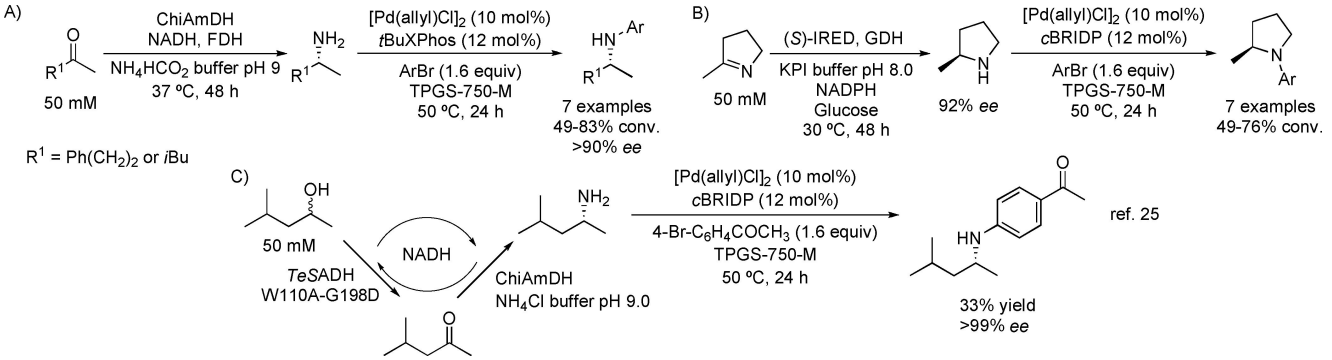
Our research group has expanded the potential of the Wacker-Tsuji oxidation for the synthesis of chiral amphetamine derivatives from allylarenes, using stereocomplementary ATAs in predominantly aqueous medium.[22] The oxidation reaction was accomplished at 30–60 °C, using palladium(II) trifluoroacetate [$Pd(TFA)_2$] with $Fe_2(SO_4)_3$ and NaTFA for the Pd^{II} regeneration. Then, the transaminase, pyridoxal-5′-phosphate (PLP), isopropylammonium phosphate, and a phosphate buffer solution containing isopropylamine (2-$PrNH_2$) were added to the reaction medium to adjust the pH around 8 for the second step. This sequential approach was carried out without any compartmentalization requirement enabling the isolation of the amines with 70–92 % and 99 % *ee* (Scheme 4B). Similarly, a metal-photo-enzymatic approach was described, developing the oxidation reaction with $PdCl_2(MeCN)_2$ and 9-mesityl-10-methylacridinium perchlorate ([Acr-Mes]ClO_4) under blue-led irradiation.[23] This methodology resulted to be compatible with the use of ADHs and ATAs after modification of the reaction conditions at the intermediate stage, obtaining both alcohols and amines with moderate to good yields and high selectivity (Scheme 4B).

2.1.3. Buchwald–Hartwig Cross-Coupling

Buchwald–Hartwig cross-coupling consists of the reaction between amines and aryl bromides in the presence of Pd catalysts.[24] The first time that it was combined with a biotransformation was the asymmetric reductive amination of different ketones using a chimeric amine dehydrogenase (ChiAmDH) followed by reaction of so-obtained chiral amines with the corresponding aryl bromides, [Pd(allyl)Cl]$_2$, ^{t}BuXPhos as ligand, NaOH, and a degassed aqueous solution of surfactant TPGS-750-M (Scheme 5A).[25] Thus, (*R*)-N-substituted amines were obtained in 49–83 % conv. and high enantiomeric excess (>90 % *ee*). In the same contribution, Turner and co-workers demonstrated the compatibility of imine reductases (IREDs) for asymmetric imine reduction with a Buchwald–Hartwig cross-coupling step, using in this case the Takasago ligand (cBRIDP, Scheme 5B). Thus, a series of enantioenriched pyrrolidines were obtained with 49–76 % conv. The possibility of coupling this arylation reaction with a biocatalytic hydrogen-borrowing amination was also explored, converting racemic 4-methylpentan-2-ol into (*R*)-1-{4-[(4-methylpentan-2-yl)-amino]phenyl}ethan-1-one using an ADH-AmDH system (Scheme 5C). However, the development of an ATA-Buchwald–Hartwig cascade could not be developed due to the presence of a competing nucleophilic amine donor (D-alanine), and was achieved in a stepwise manner. Similarly, Paradisi and co-workers have recently described a similar system using (*R*)-selective TA from *Thermomyces stellatus* for the bioamination of a series of aldehydes and ketones.[26] However, the process was performed in a stepwise manner, requiring a centrifugation for protein elimination before accomplishing the Buchwald–Hartwig reaction.



Scheme 4. Wacker-Tsuji-enzyme combinations for the synthesis of chiral alcohols and amines from alkenes.



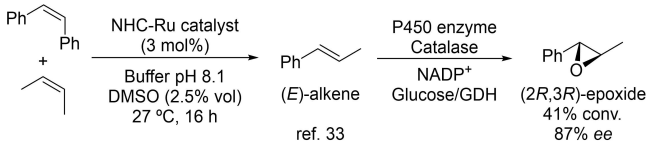
Scheme 5. Combination of Buchwald–Hartwig couplings and biocatalytic steps with an: A) AmDH; B) IRED; and C) ADH-AmDH.

2.2. Ruthenium (Ru)

Ru complexes are versatile catalysts, traditionally employed as racemization agents in DKRs,[7,27] (asymmetric) hydrogen transfer reactions,[28] and isomerizations,[29] among others. However, the most representative example of the catalytic potential of this transition metal is the olefin metathesis, which has been properly applied in chemoenzymatic cascades.

2.2.1. Olefin and Ring-Closing Metathesis

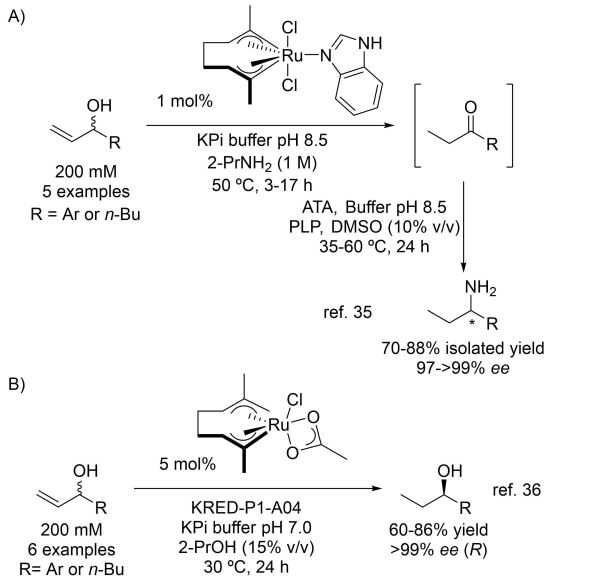
Olefin metathesis has become a powerful tool to construct new C–C bonds.[30] Despite the usefulness of this reaction to obtain alkene compounds, its combination with biocatalytic steps has been focused on non-stereoselective strategies[31] such as ring-closing metathesis.[32] Merging this reaction with a biotransformation in an asymmetric manner was for instance described by Hartwig, Zhao, and co-workers.[33] A Ru-catalyzed olefin metathesis and asymmetric enzymatic epoxidation was reported using a cytochrome P450-BM3 mutant from *Bacillus megaterium* (Scheme 6). An N-heterocyclic carbene (NHC)-Ru^{II} complex was used to accomplish the olefin cross-metathesis between (*Z*)-stilbene and (*Z*)-but-2-ene, then an engineered P450 with its cofactor and the glucose dehydrogenase (GDH) as cofactor recycling enzyme were added. The *trans*-epoxide was obtained with 41 % conv. in a concurrent approach.



Scheme 6. Ru-catalyzed cross-metathesis of (*Z*)-stilbene and (*Z*)-but-2-ene followed by bioepoxidation.

2.2.2. Isomerization and Amide Hydration

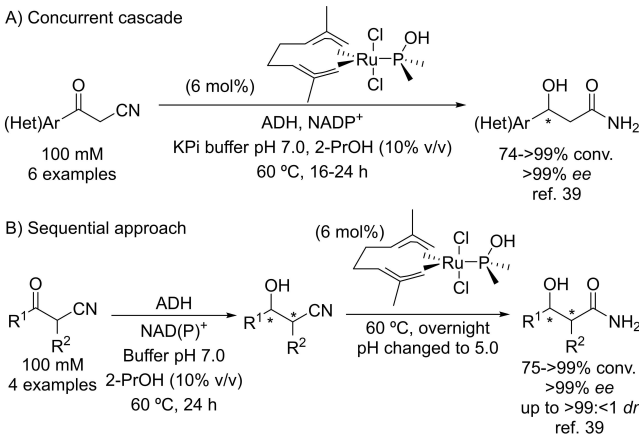
Ru complexes are also able to catalyze olefin relocations, enol-carbonyl isomerizations, or Meyer–Schuster/Rupe rearrangements.[34] This ability has not been ignored by the biocatalytic community, González-Sabín and co-workers reporting a smart strategy to synthesize enantioenriched amines from allylic alcohols.[35] The different substrate concentrations needed for each step (200 mM for the alcohol isomerization *vs* 20 mM for the bioamination), led to the design of a sequential strategy (Scheme 7A). The isomerization was performed with a small loading of the Ru catalyst (1 mol %) in aqueous medium and the presence of 2-$PrNH_2$ in excess, required as amine donor for the bioamination. A commercial ATA, PLP and additional buffer were added to carry out the transamination, successfully isolating the desired optically active amines. The same research group published a similar strategy replacing ATAs by commercial ADHs for the synthesis of chiral alcohols in



Scheme 7. Combination of a Ru-catalyzed alkene isomerization with ketone: A) biotransamination; B) bioreduction.

a concurrent cascade approach.[36] Both the isomerization of the starting allylic alcohols and the bioreduction were performed at 30 °C, obtaining the enantiopure alcohols with variable yields (Scheme 7B). The use of DES-buffer mixtures was also feasible, although the metal loading (10 mol %) and temperature (40 °C) had to be increased to achieve complete isomerizations at short reaction times.[37]

Ru complexes display high catalytic activity to perform nitrile hydration,[38] and their compatibility with ADHs was described for the preparation of chiral β-hydroxy amides.[39] A series of β-ketonitriles were hydrated using a Ru^{II} complex in aqueous media and the presence of 2-PrOH as cosolvent and hydrogen donor for carbonyl reduction. On one hand, a concurrent cascade allowed to synthesize 6 β-hydroxy amides (74–99 % conv. and > 99 % *ee*), through the combination of a Ru complex and a commercial ADH, which impressively worked at 60 °C (Scheme 8A). On the other hand, the sequential approach was developed through bioreduction of β-ketonitriles to obtain optically active β-hydroxy nitriles, adding then the Ru^{II} complex to mediate the nitrile hydration (Scheme 8B). Thus, the β-hydroxy amides were produced with excellent enantioselectivities. The sequential approach provides advantages when incomplete conversions or mismatched ADH stereoselectivities towards the β-ketonitrile/β-ketoamide pair were observed.



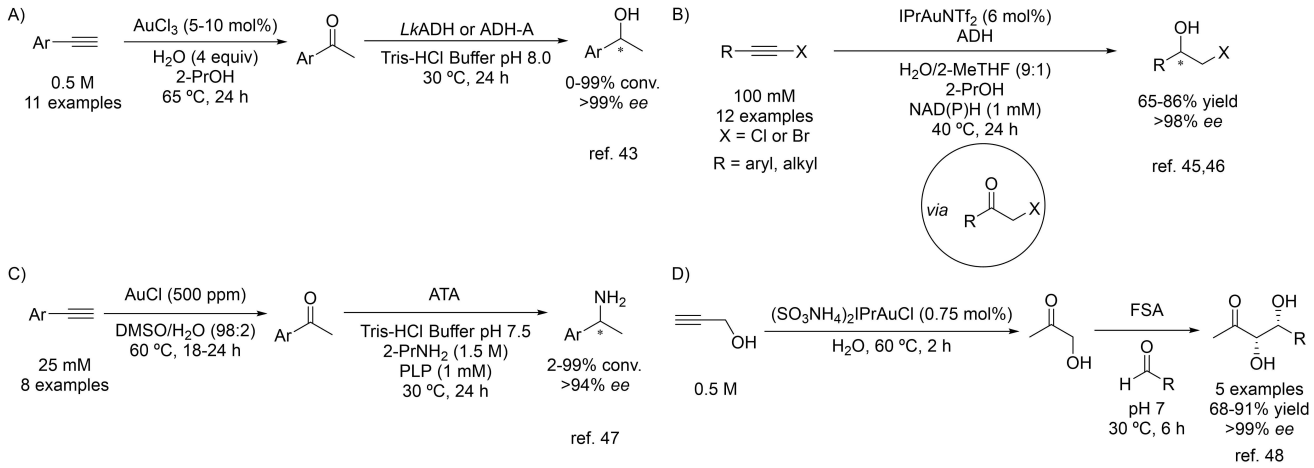
Scheme 8. Nitrile hydration and bioreduction combinations towards chiral β-hydroxy amide syntheses through: A) concurrent cascade; B) sequential approach.

2.3. Gold (Au)

In recent decades, the catalytic potential of Au in its various oxidation states has become well known, thus generating a "gold fever". Homogeneous Au catalysis offers multiple advantages such as high catalytic activity, no need for extreme reaction conditions and high selectivity tolerating different functional groups, therefore appearing as a promising strategy for organic synthesis.[40]

2.3.1. Alkyne Hydration

Hydration of triple bonds is the simplest hydrofunctionalization, as a water molecule acts as nucleophile giving rise to a carbonyl compound with 100 % atom economy.[41] Au complexes have proven to be the most effective catalysts in the activation of alkynes against the attack of nucleophiles such as water, alcohols and others due to their high π-acidity and low oxophilicity.[42] Bearing in mind this, the combination with biocatalysts has not gone unnoticed, and in recent years this area is in continuous expansion. Mihovilovic and co-workers described in 2018, a sequential process for the synthesis of several 1-arylethanols by combining an alkyne hydration of arylacetylenes with $AuCl_3$ followed by stereoselective bioreduction of the resulting acetophenones with ADHs.[43] The first step was carried out with the Au catalyst in 2-PrOH as solvent and H_2O. Then, a buffer solution at pH 8.0, the corresponding nicotinamide cofactor and *Lk*ADH or ADH-A were added. Thus, eleven enantiopure alcohols were independently accessed (Scheme 9A). Another Au-ADH cascade was also reported by García-Álvarez, González-Sabín and co-workers,[44] using $KAuCl_4$ as catalyst and commercial ADHs to obtain optically active γ-hydrox-



Scheme 9. Combination of Au-catalyzed alkyne hydrations with different biocatalytic transformations.

yvaleric acid, γ-valerolactone or a γ-hydroxy amide. In a first step, the hydration of an alkyne precursor such as pent-4-ynoic acid or *N*-tosylpent-4-ynamide was achieved in an alcohol medium or under neat conditions. Due to the inhibition of the enzymes by the gold catalyst, the reaction medium was diluted with DMSO, that acted as a ligand, and the proper buffer, attaining the desired enantiopure products in very high conversions (>96 %).

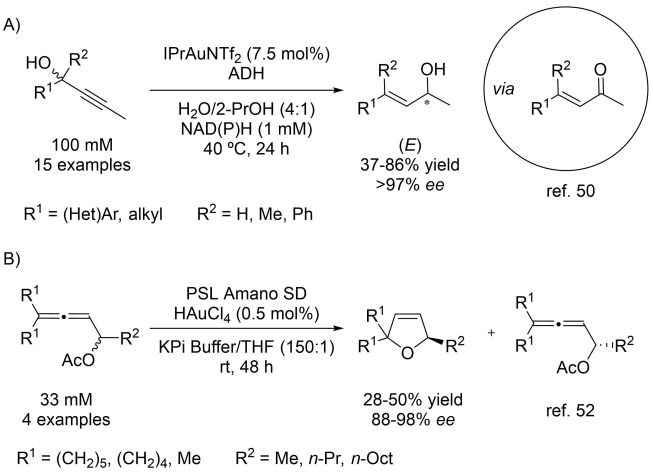
Recently, our research group has designed a concurrent cascade through the combination of a NHC-Au^I catalyst with ADHs in aqueous medium to obtain chiral halohydrins, valuable precursors for the pharmaceutical industry.[45] The metal species catalyzed the regioselective hydration of a series of aromatic haloalkynes to afford the α-halomethyl ketone intermediates, that in the presence of ADH-A or *Lactobacillus brevis* ADH (LBADH) and 2-PrOH gave access to the final enantiopure halohydrins at 40 °C. The addition of just 2 equivalents of the hydrogen donor was sufficient to achieve quantitative conversions (>99 %), because the reduction of these substrates is thermodynamically favored. This improved the synthetic applicability of the process, avoiding the formation of a by-product coming from the addition of 2-PrOH to the alkyne moiety. In addition, this method has also been recently extended to aliphatic substrates (Scheme 9B).[46]

Rueping and co-workers have described a sequential process to obtain chiral amines in this case (Scheme 9C).[47] AuCl in low loading was used for the hydration of different aromatic alkynes combined with a biotransamination. The first step was carried out at 60 °C in DMSO (98 % v/v), and then, a buffer pH 7.5, PLP, 2-$PrNH_2$ and the corresponding commercial ATA were added, giving access to the desired 1-arylethanamines in variable conv. (2–99 %) and very high selectivities (>94 % *ee*).

More recently, Guérard-Hélaine and co-workers have described a sequential approach combining a NHC-Au^I catalyst in small amounts with an aldolase for the synthesis of different monosaccharides.[48] Thus, prop-2-yn-1-ol was hydrated at 60 °C followed by an aldol condensation with different aliphatic aldehydes catalyzed by fructose-6-phosphate aldolase (FSA) at 30 °C (Scheme 9D).

2.3.2. (Cyclo)isomerization

Meyer–Schuster rearrangement is one of the most characteristic transformations that propargylic alcohols can undergo to provide α,β-unsaturated carbonyl compounds.[49] Au complexes can catalyze this reaction under mild conditions, being compatible with the reaction of ADHs and ATAs. In this context, our research group successfully developed a concurrent cascade to synthesize fifteen optically active (hetero)aryl and aliphatic (*E*)-β,β-disubstituted allylic alcohols in good yields (37–86 %).[50] The approach consisted of the transformation of racemic propargylic alcohols with a NHC-Au^I complex and ADH-A or LBADH at 40 °C in a predominantly aqueous medium and 2-PrOH as organic cosolvent and as hydrogen donor (Scheme 10A). This methodology has been expanded to the synthesis of β,β-disubstituted allylic amines by merging a similar Au^I-catalyzed rearrangement with a biotransamination step with commercial ATAs. A concurrent cascade protocol using less nucleophilic alanine as amine donor was tried, but a sequential approach worked better by addition of 2-$PrNH_2$ after the metal-catalyzed step, providing both enantiomers of eight allylic amines in moderate to high isolated yields (53–84 %).[51]



Scheme 10. Combination of an Au-catalyzed (cyclo)isomerization with different biocatalytic transformations.

In 2009, Asikainen and Krause obtained different chiral 2,5-dihydrofurans by combining a lipase-catalyzed kinetic resolution via ester hydrolysis with a subsequent Au-mediated cycloisomerization in a concurrent manner.[52] The first stage was the selective formation of an allenol catalyzed by immobilized PSL in an aqueous phosphate-buffered solution, followed by the activation of the allenol with an Au^{III} catalyst, which promoted a ring closure, providing the oxygenated cyclic compounds in moderate yields (28–50 %) and high stereoselectivities (88–98 % *ee*, Scheme 10B).

2.4. Iridium (Ir)

Over the past decades, there have been exceptional developments using Ir complexes in photochemistry,[53] since they can catalyze both oxidative or reductive transformations under excited conditions. Thus, Zhou and co-workers described the racemization of different aliphatic primary amines with an Ir^{III} catalyst under white LED in the presence of a thiol which acted as hydrogen atom transfer reagent.[54] When combined with a lipase, a DKR of these substrates could be done. To achieve this, $Ir(ppy)_2$(dtbbpy)PF_6 and *n*-octanethiol were employed in MeCN for the first step, while for the second one CAL-B and methyl 3-methoxypropanoate as acyl donor were used. After 2–6 days at 38 °C, nineteen (*R*)-amides were obtained with moderate to excellent isolated yields (58–97 %) and good to excellent *ee* values (73–99 %).

Zhao, Hartwig and co-workers have reported the successful combination of a cationic Ir^{III} complex and

EREDs from the Old Yellow Enzyme (OYE) family under blue light irradiation for an alkene photoisomerization-bioreduction sequence.[55] After light-induced isomerization between the (*Z*)- and (*E*)-forms of a series of 2-arylbut-2-enedioic acid dimethyl esters, the last isomers were transformed by the oxidoreductases (Scheme 11A). For the development of this cascade process, the alkene substrate reacted with an ERED in the presence of $[Ir(dmppy)_2(dtbbpy)]PF_6$ or flavin mononucleotide (FMN) as photocatalysts. Glucose/GDH was employed as cofactor recycling system and DMSO as cosolvent (10 % v/v). Under blue light, reduced products bearing electron-withdrawing groups were obtained in moderate to high conv. (60–96 %) and high optical purities. Interestingly, both catalysts accelerated the isomerization in a cooperative manner since a poor rate was achieved when adding the ERED after 8 h.

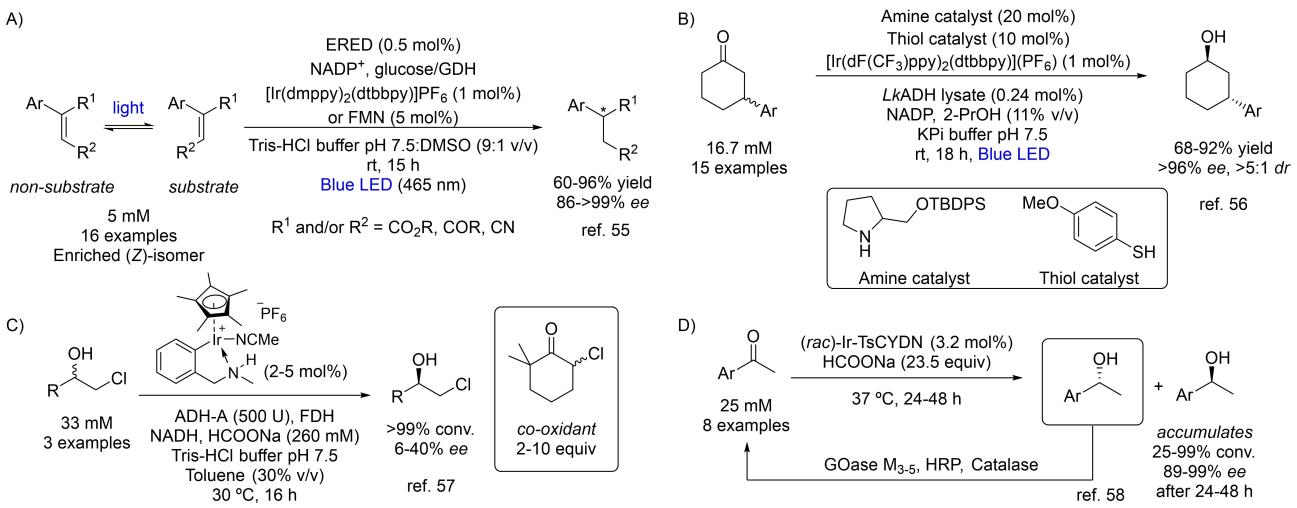
More recently, Hyster's group has demonstrated the compatibility of different biocatalysts under light conditions, expanding the development of novel photobiocatalytic systems.[56] In this case, a DKR process was developed over β-substituted ketones to obtain chiral γ-substituted amines and alcohols. While DKRs rely on inducible dynamic stereocenters, in this example the racemization proceeded in a static one. To achieve this goal, an Ir catalyst, two organocatalysts and an enzyme such as an ADH or an ATA were combined. Hence, the corresponding cyclic ketone substituted at β-position, a pyrrolidine-derived catalyst and a thiol catalyst, $[Ir(df(CF_3)ppy)_2(dtbbpy)](PF_6)$ and *Lk*ADH lysate, were incubated in a phosphate buffer including the cofactor and 2-PrOH at rt under blue LED light irradiation. Thus, the target γ-substituted alcohols were obtained with high yields (68–92 %) and enantio- and diastereomeric ratio (Scheme 11B). This method was also applied to the production of chiral amines (75–86 %) using commercial ATAs and 2-PrNH_2 as amine donor.

Ir complexes have also been applied as valuable redox agents in chemoenzymatic cyclic deracemizations. Hence, Kroutil and co-workers applied this system on β-chlorohydrins combining the action of an iridacycle complex with ADH-A (Scheme 11C).[57] Thus, the metal catalyst with an α-chloroketone as co-oxidant could oxidize the racemic substrates to the corresponding α-chloroketones which were then selectively reduced providing the enantioenriched (*R*)-alcohols under mild conditions. Unfortunately, due to the cross-reactivity between both catalytic cycles, *ee* values were usually low. However, this was a proof that Ir and enzymatic chemistries could be concurrently combined. Later, Turner and co-workers reported the deracemization of 1-arylethanols through selective enzymatic oxidation using an alcohol oxidase and a non-selective metal transfer hydrogenation process with an Ir catalyst (Scheme 11D).[58] The corresponding ketone reacted with *rac*-Ir-*N*-(*p*-toluenesulfonyl)-1,2-diaminocyclohexane (TsCYDN) and HCOONa as hydrogen donor for the reduction step. After 1.5 h at 37 °C, the desired racemic alcohol was obtained with 94 % conv. Then, a variant from (*R*)-selective galactose oxidase GOase $M_{3\text{-}5}$, horseradish peroxidase (HRP) and a catalase were added to produce the enantioselective oxidation, achieving the aromatic (*S*)-alcohols in usually high conv. (25–99 %) and *ee* (89–99 %) after 24–48 h.

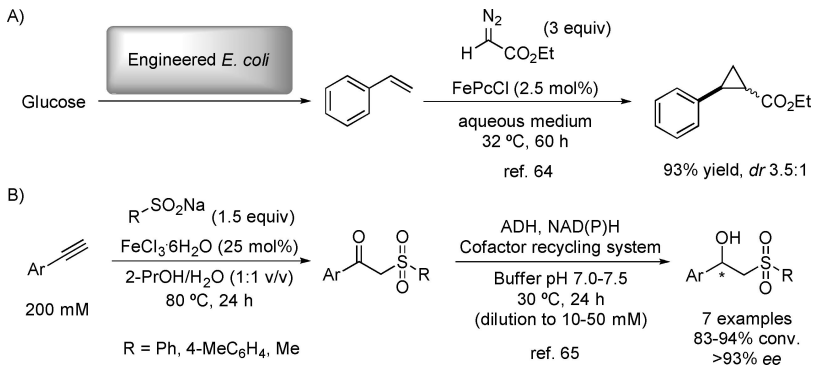
2.5. Iron (Fe)

Compared to other metals, Fe salts and complexes can be considered as non-toxic and inexpensive catalysts,[59] so in the last few years a great interest has appeared to study their synthetic applications.[60] They have been studied, for instance, when developing lipase-catalyzed DKRs on aromatic and aliphatic secondary alcohols as described by Rueping and co-workers,[61] Bäckvall's group[62] and Zhou's group,[63] using in some cases air- and moisture-stable catalysts.

Due to the capacity of Fe species to catalyze cyclopropanation reactions, Wallace and Balskus reported the use of modified *E. coli* cells that metabolized styrene into D-glucose, followed by the reaction of a biocompatible Fe^{III} phthalocyanine catalyst (FePcCl, Scheme 12A).[64] After



Scheme 11. Combinations of Ir (photo)catalyzed transformations with different biocatalytic reactions.



Scheme 12. Combinations of Fe-catalyzed transformations with different biocatalytic reactions.

individual reaction optimization, the cyclopropanation of styrene was performed with, e.g. ethyl diazoacetate in the presence of FePcCl, producing ethyl 2-phenylcyclopropane-1-carboxylate (*cis*:*trans* 3.5:1 ratio) in 93 % isolated yield after 60 h.

Very recently, our research group has described the synthesis of chiral β-hydroxy sulfones via Fe-catalyzed oxosulfonylation of a series of arylacetylenes followed by bioreduction of the β-ketosulfone intermediates in a sequential approach (Scheme 12B).[65] After reaction optimization, $FeCl_3 \cdot 6H_2O$ was selected as catalyst. The corresponding alkyne reacted with a sodium sulfinate salt in a mixture of 2-PrOH and water (1:1 v/v) at 80 °C for 24 h. Then, an ADH from a commercial source or the one from *Ras*ADH, the cofactor and the buffer were added to the reaction medium, to accomplish the stereoselective reduction of the intermediates at 30 °C for 24 h, affording the desired enantioenriched alcohols (83–94 % conv.). This chemoenzymatic approach is highly advisable due to the instability of the ketone intermediates, especially when their purifications were considered.

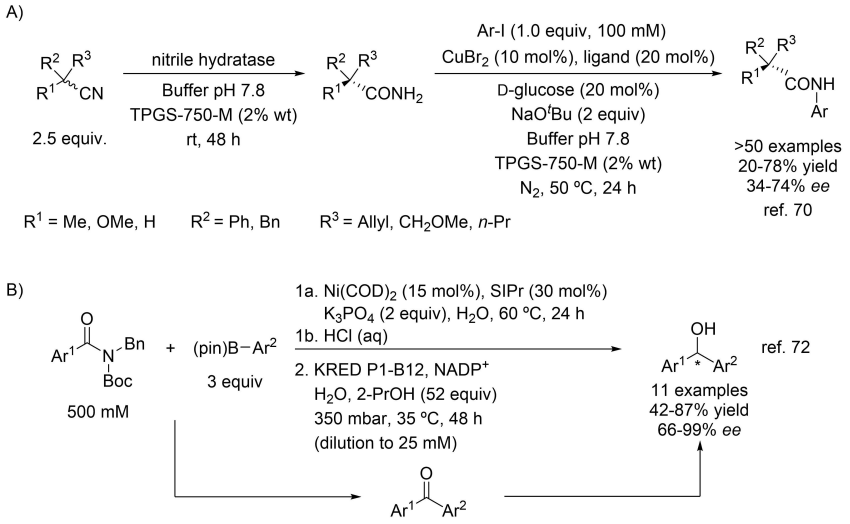
2.6. Miscellaneous

The use of other metal species from Cu, Ni, Rh, Pt and Co has attracted less attention for the design of metalloenzymatic cascades, although they have multiple applications in redox transformations. For instance, Cu salts are very useful in reactions such as Wacker-Tsuji oxidations (as co-oxidants, in stoichiometric amount),[21] cycloadditions of alkynes and azides (in catalytic amount),[66] or Sonogashira couplings (in catalytic amount).[67] However, in some cases, it has been described that these species can inhibit the enzymatic activities.[68] Nevertheless, they have found applications in chemoenzymatic sequential approaches. Kourist and co-workers developed an asymmetric decarboxylation of prochiral aliphatic arylmalonate derivatives using stereocomplementary variants of arylmalonate decarboxylase from *Bordetella bronchiseptica*, followed by alkene reduction using $CuCl_2$ as catalyst (10 mol %) and diimide as reductant.[69] The use of this hydrogen donor was essential to avoid the loss of the optical purity of the α-substituted carboxylic acid intermediates. For instance, (*R*)-2-methylbutanoic acid was isolated with 98 % *ee* and 83 % yield.

In a very recent contribution, Micklefield and co-workers have combined the reaction of a nitrile hydratase with a Cu salt to synthesize N-arylated amides from nitrile compounds (Scheme 13A).[70] Different variants from a nitrile hydratase from *Rhodococcus equi* were tested on aromatic, aliphatic and racemic nitrile compounds, obtaining the corresponding amides with high conversions and stereoselectivities in phosphate buffer with 2-PrOH (10 % vol) or a surfactant (TPGS-750-M, 2 % wt) at rt after 24–48 h. Then, $CuBr_2$, *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine as ligand, D-glucose as reductant, NaO^{t}Bu as base, and an iodoarene, were added to achieve the Ullmann-type arylation of the amide at 50 °C for 24 h in moderate to high yields. More than fifty examples were described, including racemic nitriles, giving rise to the enantioenriched N-aryl amides (20–78 % isolated yield) through kinetic resolution.

In addition to Pd species, Ni catalysts are also able to catalyze Suzuki–Miyaura couplings.[71] Garg and co-workers developed a one-pot sequential chemoenzymatic approach to yield enantioenriched alcohols starting from amides.[72] The key to this set-up was a Ni-catalyzed Suzuki–Miyaura reaction in aqueous medium, which is uncommon, to later combine it with a bioreduction process. The coupling between an aromatic amide and an arylboronate was accomplished by $Ni(COD)_2$ in the presence of 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidine (SIPr) as ligand and K_3PO_4 as base in water at 60 °C during 24 h. After quenching the reaction, the diaryl ketone intermediates were reduced using a commercial ketoreductase (KRED), in the presence of the cofactor and 2-PrOH. Also, water was added to dilute the reaction, and the equilibrium was shifted by lowering the pressure (thus removing the acetone co-product). After 48 h at 35 °C, eleven alcohols were synthesized in moderate to high yields (42–87 %) and selectivities (66–99 % *ee*, Scheme 13B).

Other metals that have been recently used in chemoenzymatic transformations are Rh,[73] Pt,[74] and Co.[75] However, these reactions were performed in a telescopic or in a non-stereoselective fashion, out of the scope of this minireview, although it is expected that in the close future



Scheme 13. Use of Cu and Ni species in chemoenzymatic cascades: A) Merging a nitrile hydratase and a Cu-catalyzed Ullmann-type arylation to synthesize chiral N-aryl amides. B) Merging a Ni-catalyzed Suzuki–Miyaura coupling and ADH to obtain enantioenriched diaryl alcohols.

examples of asymmetric cascades using these metals will be described.[76]

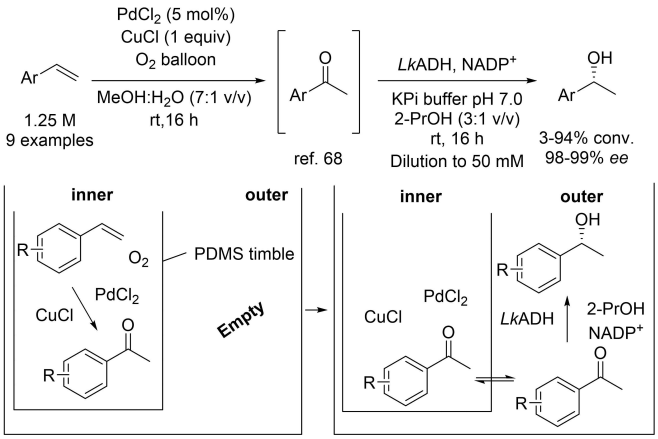
3. Strategies to Improve the Compatibility Between Metals and Enzymes

As pointed out before, the combination of (at least) two different types of catalysts needs a careful study of the reaction conditions, to find suitable (or at least acceptable) ones that can work for every reaction step involved in the process. The easiest way is a "telescoped" approach, where a reaction crude obtained from a stage is used as starting material for the next one. However, it is desirable to avoid such time- and energy-consuming protocols, if possible. Therefore, chemists have envisaged different solutions if a concurrent chemoenzymatic transformation cannot be done due to catalyst(s), auxiliary reagent(s) or reaction conditions incompatibilities. In some cases, the use of a compartmentalized system (resembling what occurs in living cells), by segregating the reactions which are incompatible in different compartments, has largely improved the outcome of the cascade process.[77]

Since enzymatic transformations occur in water while metal catalysis usually works in organic media, at first sight the use of biphasic systems adding an immiscible solvent could be envisaged as a solution. In fact, it has been successfully applied in, e.g. the Pd-mediated Buchwald–Hartwig amination of chiral amines obtained after ATA-catalyzed biotransamination,[26] or in enzymatic halocyclizations using a haloperoxidase combined with a Pd-catalyzed Suzuki-type cross coupling.[78] However, the interactions among the different species are not completely avoided in the reaction medium, and can be problematic when isolating the final products.[77]

Another way to physically separate different components is using polydimethylsiloxane (PDMS) thimbles as described by Gröger and co-workers in the combination of Wacker-Tsuji oxidation and enzymatic steps. To overcome the enzymatic inhibition observed due to the Cu salt used as co-oxidant, the compartmentalization of both reactions was developed, achieving first the Wacker-Tsuji oxidation inside the thimble, and then, *Lk*ADH, the cofactor and the buffer were added in the outer part. Finally, the chiral alcohols could be obtained in good conversions (Scheme 14).[68] This strategy has also been successfully applied when Wacker-Tsuji oxidations were combined with other enzymes such as ATAs[79] and AmDHs,[80] or when a Pd-catalyzed Liebeskind-Srogl cross-coupling reaction was merged with ADHs.[81]

Also, the use of detergents or surfactants has been successfully applied to form micelles in water, providing a medium to make possible organic transformations in an



Scheme 14. Chemoenzymatic Pd-ADH cascade employing a PDMS thimble for compartmentalization.

aqueous environment (Scheme 15A). In this field, Lipshutz's group has been especially active, describing different metalloenzymatic processes in the presence of surfactants. For instance, combinations of Pd- (Heck and Sonogashira reactions) or Au-mediated (hydration of alkynes) reactions with ADH-catalyzed bioreductions were demonstrated.[82] DL-α-Tocopherol methoxypolyethylene glycol succinate (TPGS-750-M, 2 % wt, Scheme 15B)[83] was employed as surfactant to carry out the metal cross-coupling or hydration in aqueous medium. Thus, several enantiopure alcohols were synthesized. This strategy,[25,70] has also been successfully implemented to a one-pot sequence Suzuki–Miyaura cross-coupling followed by an alkene bioreduction.[84]

Another approach to compartmentalize a reaction system is via encapsulation of some of the reagents or catalysts to provide a different environment that can be advantageous for developing a cascade transformation. For instance, in DKRs it is common to encapsulate one of the catalysts to avoid undesired interferences, as in the example described by Li and co-workers, where they encapsulated Pd nanoparticles in a metal organic framework to perform the DKR of racemic amines with CAL-B.[85] Regarding chemoenzymatic linear cascades, Toste et al. showed the resolution of a series of allenic esters to obtain enantioenriched tetrahydrofurans, using PSL to carry out the hydrolysis of the ester group of the substrate, affording an allenol that was activated by Me_3PAu^+ encapsulated in a tetrahedral gallium cluster, providing the products in moderate conversions and high selectivities.[86] This reaction proceeded in a concurrent manner in aqueous medium, since the encapsulation prevented the inactivation of the Au catalyst by the enzyme.

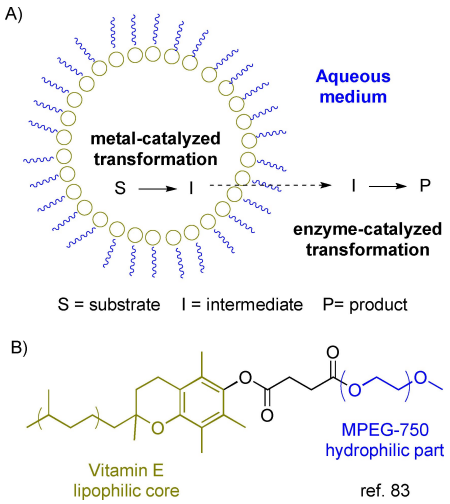
Very recently, Liu and co-workers reported the encapsulation of a NHC-Au^I catalyst (IPrAuOTf) in mesoporous silica nanoparticles, to achieve the hydration of several propargyl ethers, which underwent reductive amination by the action of amine dehydrogenase from *Geobacillus kaustophilus* (*Gk*AmDH), in the presence of ammonium formate as both amine and hydrogen donor source to recycle the nicotinamide cofactor with formate dehydrogenase (FDH). After derivatization, the corresponding (*R*)-amides were obtained with very high isolated yields (78–98 %) and optical purities (>95 % *ee*, Scheme 16).[87]

The development of compartmentalization strategies for metal-enzyme cascades due to inherent existing incompatibilities between both catalysis, has largely increased the interest of research groups during the last decades. This has been especially noticeable for Pd chemistry or aminating enzymes that need high loadings of nucleophilic amine donors. While the use of more straightforward methods such as biphasic systems or the addition of surfactants have led to excellent results in some cases, it cannot be ignored that cross-inhibitions might still be present and downstream process can be problematic. Other approaches such as the use of thimbles or encapsulations will physically separate better the mismatched components, however, the set-up of these systems is more complex and can be incompatible with a desired solvent medium. In any case, concrete applications at larger scale for these strategies must still be demonstrated.

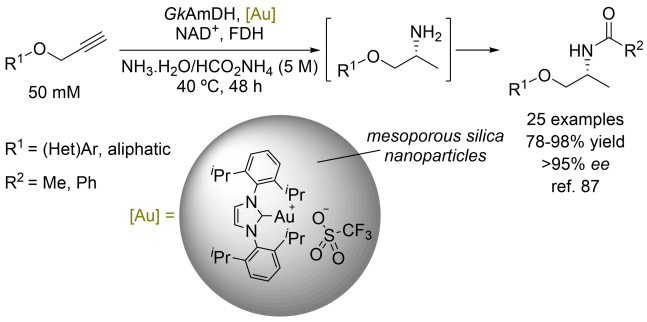
4. Summary and Outlook

The cooperative action of metals and enzymes is gaining increasing attention due to the possibility to perform straightforward stereoselective linear cascades for the valorization of raw materials. To achieve this aim, this minireview has summarized remarkable achievements in this field demonstrating that both catalytic worlds can be efficiently combined. The use of concurrent cascades remains the simplest way to set-up these transformations, while sequential approaches are recommended when catalyst incompatibilities are found, or different scenarios are required for the best performance of both catalyst types. In addition, the use of surfactants and the design of compartmentalization strategies provide additional advantages that can be used to solve catalyst incompatibilities. In this context, the use of bionanohybrids is starting to have a representative role in chemoenzymatic protocols,[88] especially for DKRs, although other cascades have been recently considered.[89]

On one hand, Pd, Ru, Ir and Fe species have expanded their synthetic possibilities moving from traditional racemi-



Scheme 15. A) Example of a chemoenzymatic cascade using a surfactant for compartmentalization; B) Structure of TPGS-750-M.



Scheme 16. Encapsulation of an Au catalyst to achieve a chemoenzymatic cascade with an AmDH to synthesize chiral amines.

zation roles to the catalysis of striking C–C bond formation, isomerizations and oxidative processes, among others. However, combination of Au complexes with different enzyme classes is acquiring great relevance in recent years due to its easy combination with ADHs, aldolases, AmDHs, ATAs and lipases for the synthesis of chiral amines, alcohols and hydroxy ketones. On the other hand, the versatility of Cu, Ni, Rh, Pt and Co opens new possibilities in chemoenzymatic cascades. This is especially attractive when non-precious metals are considered,[90] where Ni catalysis will have a prominent role in the next years.

Overall, the synthetic possibilities of merging metal and enzyme catalysis have been demonstrated in the last decades. Next efforts should be made to develop scalable and robust processes that will provide solutions for industrial applications in asymmetric synthesis.[91]

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Conflict of Interest

The authors declare no conflict of interest.

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[1] a) R. Roddan, E. M. Carter, B. Thair, H. C. Hailes, *Nat. Prod. Rep.* **2022**, *39*, 1375–1382; b) C. K. Winkler, J. H. Schrittwieser, W. Kroutil, *ACS Cent. Sci.* **2021**, *7*, 55–71; c) L. E. Zetzsche, S. Chakrabarty, A. R. H. Narayan, *J. Am. Chem. Soc.* **2022**, *144*, 5214–5225; d) U. Hanefeld, F. Hollmann, C. E. Paul, *Chem. Soc. Rev.* **2022**, *51*, 594–627.

[2] a) R. A. Sheldon, D. Brady, *ACS Sustainable Chem. Eng.* **2021**, *9*, 8032–8052; b) D. Yi, T. Bayer, C. P. S. Badenhorst, S. Wu, M. Doerr, M. Höhne, U. T. Bornscheuer, *Chem. Soc. Rev.* **2021**, *50*, 8003–8049; c) E. L. Bell, W. Finnigan, S. P. France, A. P. Green, M. A. Hayes, L. J. Hepworth, S. L. Lovelock, H. Niikura, S. Osuna, E. Romero, K. S. Ryan, N. J. Turner, S. L. Flitsch, *Nat. Rev. Methods Primers* **2021**, *1*, 46; d) S. Simić, E. Zukić, L. Schmermund, K. Faber, C. K. Winkler, W. Kroutil, *Chem. Rev.* **2022**, *122*, 1052–1126.

[3] a) J. Muschiol, C. Peters, N. Oberleitner, M. D. Mihovilovic, U. T. Bornscheuer, F. Rudroff, *Chem. Commun.* **2015**, *51*, 5798–5811; b) J. H. Schrittwieser, S. Velikogne, M. Hall, W. Kroutil, *Chem. Rev.* **2018**, *118*, 270–348; c) S. Schmidt, K. Castiglione, R. Kourist, *Chem. Eur. J.* **2018**, *24*, 1755–1768; d) A. I. Benítez-Mateos, D. R. Padrosa, F. Paradisi, *Nat. Chem.* **2022**, *14*, 489–499.

[4] a) Y. Wang, H. Zhao, *Catalysts* **2016**, *6*, 194; b) N. Ríos-Lombardía, J. García-Álvarez, J. González-Sabín, *Catalysts* **2018**, *8*, 75; c) F. Rudroff, M. D. Mihovilovic, H. Gröger, R. Snajdrova, H. Iding, U. T. Bornscheuer, *Nat. Catal.* **2018**, *1*, 12–22; d) X. Huang, M. Cao, H. Zhao, *Curr. Opin. Chem. Biol.* **2020**, *55*, 161–170; e) E. Heuson, F. Dumeignil, *Catal. Sci. Technol.* **2020**, *10*, 7082–7100; f) Y. Liu, P. Liu, S. Gao, Z. Wang, P. Luan, J. González-Sabín, Y. Jing, *Chem. Eng. Technol.* **2021**, *420*, 127659; g) L. Bering, J. Thompson, J. Micklefield, *Trends Chem.* **2022**, *4*, 392–408.

[5] C. Ascaso-Alegre, J. Mangas-Sánchez, *Eur. J. Org. Chem.* **2022**, e202200093.

[6] Y. Peng, Z. Chen, J. Xu, Q. Wu, *Org. Process Res. Dev.* **2022**, *26*, 1900–1913.

[7] a) O. Långvik, T. Saloranta, D. Y. Murzin, R. Leino, *ChemCatChem* **2015**, *7*, 4004–4015; b) O. Verho, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2015**, *137*, 3996–4009; c) L.-C. Yang, H. Deng, H. Renata, *Org. Process Res. Dev.* **2022**, *26*, 1925–1943.

[8] a) E. Geist, A. Kirschning, T. Schmidt, *Nat. Prod. Rep.* **2014**, *31*, 441–448; b) A. Remmel, *Nature* **2022**, *606*, 448–451.

[9] A. N. Parvulescu, P. A. Jacobs, D. E. De Vos, *Chem. Eur. J.* **2007**, *13*, 2034–2043.

[10] a) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 9047–9050; *Angew. Chem.* **2010**, *122*, 9231–9234; b) C. C. C. J. Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085; *Angew. Chem.* **2012**, *124*, 5150–5174.

[11] B. S. Kadu, *Catal. Sci. Technol.* **2021**, *11*, 1186–1221.

[12] E. Burda, W. Hummel, H. Gröger, *Angew. Chem. Int. Ed.* **2008**, *47*, 9551–9554; *Angew. Chem.* **2008**, *120*, 9693–9696.

[13] D. González-Martínez, V. Gotor, V. Gotor-Fernández, *ChemCatChem* **2019**, *11*, 5800–5807.

[14] R. Kourist, J. González-Sabín, *ChemCatChem* **2020**, *12*, 1903–1912.

[15] J. Paris, N. Ríos-Lombardía, F. Morís, H. Gröger, J. González-Sabín, *ChemCatChem* **2018**, *10*, 4417–4423.

[16] P. Luan, Y. Liu, Y. Li, R. Chen, C. Huang, J. Gao, F. Hollmann, Y. Jiang, *Green Chem.* **2021**, *23*, 1960–1964.

[17] S. T. Ahmed, F. Parmeggiani, N. J. Weise, S. L. Flitsch, N. J. Turner, *ACS Catal.* **2015**, *5*, 5410–5413.

[18] A. W. H. Dawood, J. Bassut, R. O. M. A. de Souza, U. T. Bornscheuer, *Chem. Eur. J.* **2018**, *24*, 16009–16013.

[19] J. Paris, A. Telzerow, N. Ríos-Lombardía, K. Steiner, H. Schwab, F. Morís, H. Gröger, J. González-Sabín, *ACS Sustainable Chem. Eng.* **2019**, *7*, 5486–5493.

[20] a) S. E. Mann, L. Benhamou, T. D. Sheppard, *Synthesis* **2015**, *47*, 3079–3117; b) T. V. Baiju, E. Gravel, E. Doris, I. N. N. Namboothiri, *Tetrahedron Lett.* **2016**, *57*, 3993–4000; c) R. A. Fernandes, A. K. Jha, P. Kumar, *Catal. Sci. Technol.* **2020**, *10*, 7448–7470.

[21] I. Schnapperelle, W. Hummel, H. Gröger, *Chem. Eur. J.* **2012**, *18*, 1073–1076.

[22] D. González-Martínez, V. Gotor, V. Gotor-Fernández, *Adv. Synth. Catal.* **2019**, *361*, 2582–2593.

[23] J. Albarrán-Velo, V. Gotor-Fernández, I. Lavandera, *Adv. Synth. Catal.* **2021**, *363*, 4096–4108.

[24] P. A. Forero-Cortés, A. M. Haydl, *Org. Process Res. Dev.* **2019**, *23*, 1478–1483.

[25] S. C. Cosgrove, M. P. Thompson, S. T. Ahmed, F. Parmeggiani, N. J. Turner, *Angew. Chem. Int. Ed.* **2020**, *59*, 18156–18160; *Angew. Chem.* **2020**, *132*, 18313–18317.

[26] C. M. Heckmann, F. Paradisi, *Chem. Eur. J.* **2021**, *27*, 16616–16620.

[27] a) J. Lee, Y. Oh, Y. K. Choi, E. Choi, K. Kim, J. Park, M.-J. Kim, *ACS Catal.* **2015**, *5*, 683–689; b) S. Hilker, D. Posevins, C. R. Unelius, J.-E. Bäckvall, *Chem. Eur. J.* **2021**, *27*, 15623–15627.

[28] D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621–6686.

[29] V. Cadierno, P. Crochet, J. Gimeno, *Synlett* **2008**, 1105–1124.

[30] R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117–7140.

[31] Selected examples: a) K. Tenbrink, M. Seßler, J. Schatz, H. Gröger, *Adv. Synth. Catal.* **2011**, *353*, 2363–2367; b) S. Bojarra,

D. Reichert, M. Grote, Á. Gómez Baraibar, A. Dennig, B. Nidetzky, C. Mügge, R. Kourist, *ChemCatChem* **2018**, *10*, 1192–1201; c) C. J. Hastings, N. P. Adams, J. Bushi, S. J. Kolb, *Green Chem.* **2020**, *22*, 6187–6193; d) R. V. Maaskant, S. Chordia, G. Roelfes, *ChemCatChem* **2021**, *13*, 1607–1613.

[32] a) N. Scalacci, G. W. Black, G. Mattedi, N. L. Brown, N. J. Turner, D. Castagnolo, *ACS Catal.* **2017**, *7*, 1295–1300; b) J. Pauly, H. Gröger, A. V. Patel, *ChemCatChem* **2019**, *11*, 1503–1509; c) C. Risi, F. Zhao, D. Castagnolo, *ACS Catal.* **2019**, *9*, 7264–7269; d) S. Wu, Y. Zhou, D. Gerngross, M. Jeschek, T. R. Ward, *Nat. Commun.* **2019**, *10*, 5060.

[33] C. A. Denard, M. J. Bartlett, Y. Wang, L. Lu, J. F. Hartwig, H. Zhao, *ACS Catal.* **2015**, *5*, 3817–3822.

[34] D. Fiorito, S. Scaringi, C. Mazet, *Chem. Soc. Rev.* **2021**, *50*, 1391–1406.

[35] N. Ríos-Lombardía, C. Vidal, M. Cocina, F. Morís, J. García-Álvarez, J. González-Sabín, *Chem. Commun.* **2015**, *51*, 10937–10940.

[36] N. Ríos-Lombardía, C. Vidal, E. Liardo, F. Morís, J. García-Álvarez, J. González-Sabín, *Angew. Chem. Int. Ed.* **2016**, *55*, 8691–8695; *Angew. Chem.* **2016**, *128*, 8833–8837.

[37] L. Cicco, N. Ríos-Lombardía, M. J. Rodríguez-Álvarez, F. Morís, F. M. Perna, V. Capriati, J. García-Álvarez, J. González-Sabín, *Green Chem.* **2018**, *20*, 3468–3475.

[38] a) K. Yamaguchi, M. Matsushita, N. Mizuno, *Angew. Chem. Int. Ed.* **2004**, *43*, 1576–1580; *Angew. Chem.* **2004**, *116*, 1602–1606; b) B. Kang, Z. Fu, S. H. Hong, *J. Am. Chem. Soc.* **2013**, *135*, 11704–11707; c) S. Yadav, R. Gupta, *Inorg. Chem.* **2022**, *61*, 15463–15474.

[39] E. Liardo, R. González-Fernández, N. Ríos-Lombardía, F. Morís, J. García-Álvarez, V. Cadierno, P. Crochet, F. Rebolledo, J. González-Sabín, *ChemCatChem* **2018**, *10*, 4676–4682.

[40] a) M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev.* **2012**, *41*, 2448–2462; b) B. Ranieri, I. Escofet, A. M. Echavarren, *Org. Biomol. Chem.* **2015**, *13*, 7103–7118.

[41] a) L. Hintermann, A. Labonne, *Synthesis* **2007**, 1121–1150; b) W. E. Brenzovich Jr., *Angew. Chem. Int. Ed.* **2012**, *51*, 8933–8935; *Angew. Chem.* **2012**, *124*, 9063–9065.

[42] R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028–9072.

[43] P. Schaaf, V. Gojic, T. Bayer, F. Rudroff, M. Schnürch, M. D. Mihovilovic, *ChemCatChem* **2018**, *10*, 920–924.

[44] M. J. Rodríguez-Álvarez, N. Ríos-Lombardía, S. Schumacher, D. Pérez-Iglesias, F. Morís, V. Cadierno, J. García-Álvarez, J. González-Sabín, *ACS Catal.* **2017**, *7*, 7753–7759.

[45] S. González-Granda, L. Escot, I. Lavandera, V. Gotor-Fernández, *ACS Catal.* **2022**, *12*, 2552–2560.

[46] L. Escot, S. González-Granda, V. Gotor-Fernández, I. Lavandera, *Org. Biomol. Chem.* **2022**, *20*, 9650–9658.

[47] S. Mathew, A. Sagadevan, D. Renn, M. Rueping, *ACS Catal.* **2021**, *11*, 12565–12569.

[48] C. Gastaldi, G. Mekhloufi, C. Forano, A. Gautier, C. Guérard-Hélaine, *Green Chem.* **2022**, *24*, 3634–3639.

[49] a) K. H. Meyer, K. Schuster, *Chem. Ber.* **1922**, *55*, 819; b) D. A. Engel, G. B. Dudley, *Org. Biomol. Chem.* **2009**, *7*, 4149–4158; c) V. Cadierno, P. Crochet, S. E. García-Garrido, J. Gimeno, *Dalton Trans.* **2010**, *39*, 4015–4031.

[50] S. González-Granda, I. Lavandera, V. Gotor-Fernández, *Angew. Chem. Int. Ed.* **2021**, *60*, 13945–13951; *Angew. Chem.* **2021**, *133*, 14064–14070.

[51] S. González-Granda, N. V. Tzouras, S. P. Nolan, I. Lavandera, V. Gotor-Fernández, *Adv. Synth. Catal.* **2022**, *364*, 3856–3866.

[52] M. Asikainen, N. Krause, *Adv. Synth. Catal.* **2009**, *351*, 2305–2309.

[53] K. Teegardin, J. I. Day, J. Chan, J. Weaver, *Org. Process Res. Dev.* **2016**, *20*, 1156–1163.

[54] Q. Yang, F. Zhao, N. Zhang, M. Liu, H. Hu, J. Zhang, S. Zhou, *Chem. Commun.* **2018**, *54*, 14065–14068.

[55] Z. C. Litman, Y. Wang, H. Zhao, J. F. Hartwig, *Nature* **2018**, *560*, 355–359.

[56] J. S. DeHovitz, Y. Y. Loh, J. A. Kautzky, K. Nagao, A. J. Meichan, M. Yamauchi, D. W. C. MacMillan, T. K. Hyster, *Science* **2020**, *369*, 1113–1118.

[57] F. G. Mutti, A. Orthaber, J. H. Schrittwieser, J. G. de Vries, R. Pietschnig, W. Kroutil, *Chem. Commun.* **2010**, *46*, 8046–8048.

[58] B. Yuan, D. P. Debecker, X. Wu, J. Xiao, Q. Fei, N. J. Turner, *ChemCatChem* **2020**, *12*, 6191–6195.

[59] a) K. S. Egorova, V. P. Ananikov, *Angew. Chem. Int. Ed.* **2016**, *55*, 12150–12162; *Angew. Chem.* **2016**, *128*, 12334–12347; b) K. S. Egorova, V. P. Ananikov, *Organometallics* **2017**, *36*, 4071–4090.

[60] a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254; b) I. Bauer, H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170–3387; c) A. Fürstner, *ACS Cent. Sci.* **2016**, *2*, 778–789; d) A. Casnati, M. Lanzi, G. Cera, *Molecules* **2020**, *25*, 3889.

[61] O. El-Sepelgy, N. Alandini, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, *55*, 13602–13605; *Angew. Chem.* **2016**, *128*, 13800–13803.

[62] K. P. J. Gustafson, A. Guðmundsson, K. Lewis, J.-E. Bäckvall, *Chem. Eur. J.* **2017**, *23*, 1048–1051.

[63] Q. Yang, N. Zhang, M. Liu, S. Zhou, *Tetrahedron Lett.* **2017**, *58*, 2487–2489.

[64] S. Wallace, E. P. Balskus, *Angew. Chem. Int. Ed.* **2015**, *54*, 7106–7109; *Angew. Chem.* **2015**, *127*, 7212–7215.

[65] M. López-Agudo, N. Ríos-Lombardía, J. González-Sabín, I. Lavandera, V. Gotor-Fernández, *ChemSusChem* **2022**, *15*, e202101313.

[66] a) A. Cuetos, F. R. Bisogno, I. Lavandera, V. Gotor, *Chem. Commun.* **2013**, *49*, 2625–2627; b) C. Aguirre-Pranzoni, R. D. Tosso, F. R. Bisogno, M. Kurina-Sanz, A. A. Orden, *Process Biochem.* **2019**, *79*, 114–117; c) M. Breugst, H.-S. Reissig, *Angew. Chem. Int. Ed.* **2020**, *59*, 12293–12307; *Angew. Chem.* **2020**, *132*, 12389–12404.

[67] R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874–922.

[68] H. Sato, W. Hummel, H. Gröger, *Angew. Chem. Int. Ed.* **2015**, *54*, 4488–4492; *Angew. Chem.* **2015**, *127*, 4570–4574.

[69] J. Enoki, C. Mügge, D. Tischler, K. Miyamoto, R. Kourist, *Chem. Eur. J.* **2019**, *25*, 5071–5076.

[70] L. Bering, E. J. Craven, S. A. S. Thomas, S. A. Shepherd, J. Micklefield, *Nat. Commun.* **2022**, *13*, 380.

[71] a) S. Bhakta, T. Ghosh, *Eur. J. Org. Chem.* **2021**, 4201–4215; b) D. P. Satpute, G. N. Vaidya, S. K. Lokhande, S. D. Shinde, S. M. Bhujbal, D. R. Chatterjee, P. Rana, A. Venkatesh, M. Nagpure, D. Kumar, *Green Chem.* **2021**, *23*, 6273–6300.

[72] J. E. Dander, M. Giroud, S. Racine, E. R. Darzi, O. Alvizo, D. Entwistle, N. K. Garg, *Commun. Chem.* **2019**, *2*, 82.

[73] Y. Wang, M. J. Bartlett, C. A. Denard, J. F. Hartwig, H. Zhao, *ACS Catal.* **2017**, *7*, 2548–2552.

[74] A. Lancien, R. Wojcieszak, E. Cuvelier, M. Duban, P. Dhulster, S. Paul, F. Dumeignil, R. Froidevaux, E. Heuson, *ChemCatChem* **2021**, *13*, 247–259.

[75] K. S. Arias, J. M. Carceller, M. J. Climent, A. Corma, S. Iborra, *ChemSusChem* **2020**, *13*, 1864–1875.

[76] While not being involved in linear chemoenzymatic asymmetric cascades, there are examples in the literature where a Rh complex has been used for dynamic kinetic resolutions with a lipase. See, for instance: D. Koszelewski, A. Brodzka, A. Żądło, D. Paprocki, D. Trzepizur, M. Zysk, R. Ostaszewski, *ACS Catal.* **2016**, *6*, 3287–3292.

[77] R. Kourist, J. González-Sabín, in *Biocatalysis for Practitioners: Techniques, Reactions and Applications* (Eds: G. de Gonzalo, I. Lavandera), Wiley-VCH, Weinheim, **2021**, pp. 89–112.

[78] J. M. Naapuri, G. A. Åberg, J. M. Palomo, J. Deska, *ChemCatChem* **2021**, *13*, 763–769.

[79] F. Uthoff, H. Sato, H. Gröger, *ChemCatChem* **2017**, *9*, 555–558.
[80] F. Uthoff, H. Gröger, *J. Org. Chem.* **2018**, *83*, 9517–9521.
[81] P. Schaaf, T. Bayer, M. Koley, M. Schnürch, U. T. Bornscheuer, F. Rudroff, M. D. Mihovilovic, *Chem. Commun.* **2018**, *54*, 12978–12981.
[82] M. Cortés-Clerget, N. Akporji, J. Zhou, F. Gao, P. Guo, M. Parmentier, F. Gallou, J.-Y. Berthon, B. H. Lipshutz, *Nat. Commun.* **2019**, *10*, 2169.
[83] M. P. Andersson, F. Gallou, P. Klumphu, B. S. Takale, B. H. Lipshutz, *Chem. Eur. J.* **2018**, *24*, 6778–6786.
[84] N. Akporji, V. Singhania, J. Dussart-Gautheret, F. Gallou, B. H. Lipshutz, *Chem. Commun.* **2021**, *57*, 11847–11850.
[85] S. Xu, M. Wang, B. Feng, X. Han, Z. Lan, H. Gu, H. Li, H. Li, *J. Catal.* **2018**, *363*, 9–17.
[86] Z. J. Wang, K. N. Clary, R. G. Bergman, K. N. Raymond, F. D. Toste, *Nat. Chem.* **2013**, *5*, 100–103.
[87] F. Chang, C. Wang, Q. Chen, Y. Zhang, G. Liu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202114809; *Angew. Chem.* **2022**, *134*, e202114809.
[88] J. M. Palomo, *Chem. Commun.* **2019**, *55*, 9583–9589.
[89] a) L. Gao, Z. Wang, Y. Liu, P. Liu, S. Gao, J. Gao, Y. Jiang, *Chem. Commun.* **2020**, *56*, 13547–13550; b) J. M. Naapuri, N. Losada-Garcia, R. A. Rothemann, M. C. Pichardo, M. H. G. Prechtl, J. M. Palomo, J. Deska, *ChemCatChem* **2022**, *14*, e202200362.
[90] H. Wu, B. Qu, T. Nguyen, J. C. Lorenz, F. Buono, N. Haddad, *Org. Process Res. Dev.* **2022**, *26*, 2281–2310.
[91] S. Wu, R. Snajdrova, J. C. Moore, K. Baldenius, U. T. Bornscheuer, *Angew. Chem. Int. Ed.* **2021**, *60*, 88–119; *Angew. Chem.* **2021**, *133*, 89–123.

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