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The expanding landscape of metal-amino acid complexes in modern bioinspired catalysis

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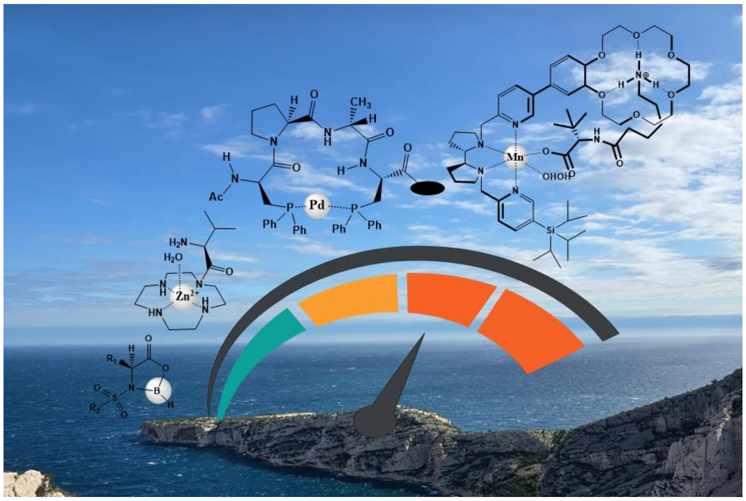
Abstract

Metal–amino acid complexes have grown into a diverse class of bioinspired catalysts. These complexes serve as a cornerstone linking enzymatic precision with synthetic chemistry. This review summarizes their development across major reaction classes. The focus is on how amino acids and their derivatives construct primary and secondary coordination spheres that significantly improve catalytic outcomes. Also, these catalytic processes emphasize mechanistic principles, such as Lewis acid activation, hydrogen bonding, and cation-π interactions. Collectively, these studies demonstrate that metal–amino acid complexes are powerful tools for sustainable and enzyme-inspired catalysis.



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1. Introduction

The development of efficient, selective, and economic catalysts has remained a long-standing challenge for synthetic chemists for decades. Such catalysts are essential not only for processes that underpin the pharmaceuticals industry[1] and agrochemicals sector,[2] but also for a wide range of non-asymmetric processes crucial to energy,[3] environmental,[4] and advanced materials science.[5] For the search for an optimum asymmetric catalyst, numerous chiral sources have been explored. Among them, amino acids have stood out due to their high abundance, low cost, structural diversity, and inherent chirality. The amino acid's role as an organocatalyst is well established.[6,7] Amino acids also serve as versatile ligands to coordinate with transition metals to form metal–amino acid complexes.[8,9]

The synthesis of metal–amino acid complex revolves around natural enzymes and synthetic catalysis. In nature, enzymes achieve extraordinary efficiency in activity and selectivity through carefully tuned coordination environments, where amino acid residues provide both metal binding and stereocontrol through first and second coordination spheres.[10] In this context, the first coordination sphere consists of amino acids directly bound to the metal center. On the other hand, the second coordination sphere includes nearby functional groups that do not coordinate the metal directly but regulate the reactivity through hydrogen bonding, electrostatic effects, steric influence, or substrate preorganization. Inspired by nature, chemists have developed artificial systems of amino acids that coordinate metal centers, which exploit the Lewis acidity and redox properties of metals. This biomimetic strategy helps to develop environmentally friendly catalysts made from simple, accessible building blocks.

Early studies revealed that metal–amino acid complexes could efficiently catalyze classical carbon–carbon bond-forming reactions, such as classical Diels–Alder[11] and aldol reactions.[12] These studies not only yielded efficiency but also answered how to achieve a highly stereoselective product. These synthetic systems draw on the Lewis acidity of metals and the chiral environment created by amino acid ligands. With time, the field has expanded beyond simple metal–amino acid complexes to include peptide-derived ligands,[13] supramolecular assemblies,[14] and metal–organic frameworks.[15]

It also underscores that metal–amino acid complexes are not restricted to only asymmetric synthesis. They are also used in diverse chemical reactions such as water splitting[16] and electrochemical CO_2 reduction.[17] These examples illustrate that the role of these complexes extends well beyond stereoselectivity, which offers strong platforms for green chemistry and sustainable catalysis.

This review is intended to provide a thorough examination of the chemistry behind metal–amino acid complexes as bio-inspired catalysts. It brings together past and recent advances across reaction types, highlighting mechanisms, structure–activity trends, and new applications. This review covers reactions of both aqueous and non-aqueous media to demonstrate the extensive adaptability of these systems and their future potential.

2. Types of metal–amino acid complexes

Metal–amino acid complexes can be classified based on their coordination mode, conformation, and structural complexity. These categories range from plain chelates to extended framework systems. Understanding these variations is crucial, as these differences strongly influence the catalytic outcome of the complexes.

2.1 First-generation metal–amino acid complexes

Each amino acid possesses at least one amine and one carboxylate moiety, which has the potential to coordinate with a metal center. The simplest metal–amino acid complexes involve coordination through the amine and/or carboxylate groups, either in a monodentate or bidentate (**1**) form [Figure 1. (a)]. Such complexes mimic natural metalloprotein active sites and provide fundamental insights into metal–ligand interactions. Those complexes showed activity in simple organic reactions, like the Diels–Alder reaction.[18] Despite their structural simplicity, these systems can induce moderate enantioselectivity while offering excellent stability and synthetic accessibility. They serve as an important platform for peptide-based and supramolecular complexes.

2.2 Second-generation metal–amino acid complexes with additional donor groups

Amino acids bearing donor groups in their side chains allow for additional coordination sites. So, complexes (**2**) with these amino acids enable multidentate binding [Figure 1. (b)].[19] These complexes have significantly enhanced electronic environment and catalytic activity. Such complexes normally mimic the active sites of metalloenzymes, where side-chain donors stabilize reactive intermediates or coordinate with metal. By fine-tuning the steric and electronic properties of the side-chain influence metal coordination, which can impact the selectivity of the reactions.

2.3 Peptide-based complexes

In this class, small peptides act as multidentate ligands to coordinate with metal. Those metal–peptide complexes (**3**) merge backbone rigidity with various side-chain functionalities of the peptide [Figure 1. (c)].[20] These complexes consist of chiral pockets around the metal center to directly replicate the enzyme's hydrophobic cavity. Peptide-based complexes have been applied in asymmetric bond-forming reactions and redox catalysis. Most of the time, these complexes surpassed the stereocontrol over simple amino acid complexes. Systematic variation of the sequence of amino acids and the length of peptides is directly related to the catalytic activity of this class.

2.4 Supramolecular and self-assembled complexes

Amino acid derivatives can self-assemble into cages and other supramolecular structures by coordinating with metal centers (**4**) [Figure 1. (d)].[21,22] For now, the catalytic study based on such architecture is limited. Like the previous class, these amino acid-derived architectures with well-defined cavities could generate unique catalytic microenvironments. Such systems have the potential to mimic enzyme structures. They could open opportunities for selective catalysis in confined spaces.

2.5 Amino acid-derived metal–organic frameworks (MOFs)

Amino acids can also be incorporated into much more extended networks, such as MOFs (**5**) [Figure 1. (e)]. These hybrid materials combine the chiral environment of amino acids with the stability, porosity, and recyclability of the framework.[15,23] In contrast with previous classes, amino acid-based MOFs have been used in catalytic reactions in recent times. Their tunable pores allow size- and shape-selective transformations, while solid-state stability and recyclability make them attractive for industrial applications.

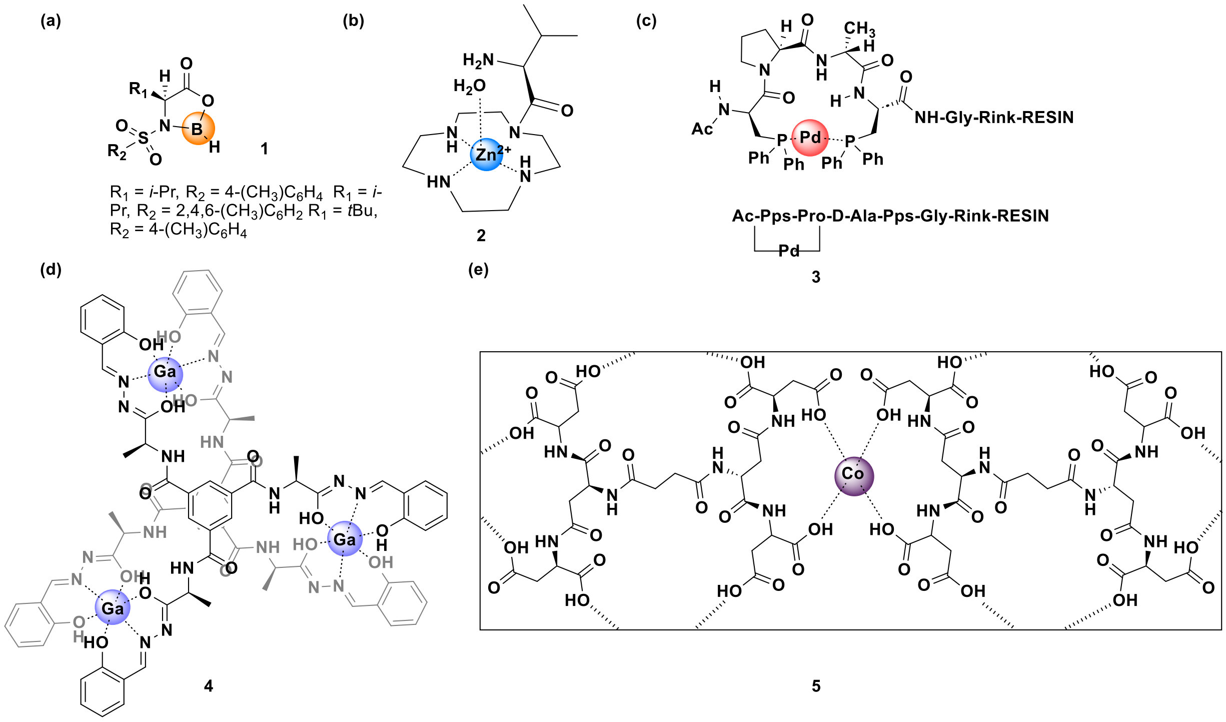


Figure 1. Different classes of metal–amino acid complexes, (a) first generation N-sulphonylamino acid ligand-boron complexes (**1**), (b) second generation complexes (**2**) with Zn and amino acid, (c) peptide-based complexes (**3**), (d) amino acid functionalized supramolecular cage (**4**), (e) close-up of Co embedded metal–organic frameworks (**5**).

3. Reaction catalyzed by metal–(amino acid/peptide) complexes

Long before metal–amino acid complexes were widely explored and classified as chiral catalysts, Belokon and co-workers developed a novel family of Ni complexes of glycine and related amino acids.[24] That enabled the highly enantioselective synthesis of tailor-made α-amino acids by alkylation and Michael-type additions. These catalytic systems behave as chiral auxiliaries as well as metal–ligand complexes. Subsequent alkylation or conjugate-addition steps followed by decomplexation provide a broad range of non-natural amino acids in excellent optical purity. This research showcased how metal–amino acid architectures can mediate stereocontrolled C–C bond formation and, at the same time, generate new amino acid building blocks.

As the field expanded, numerous metal–amino acid and metal–peptide complexes emerged, each enabling a growing range of catalytic transformations.

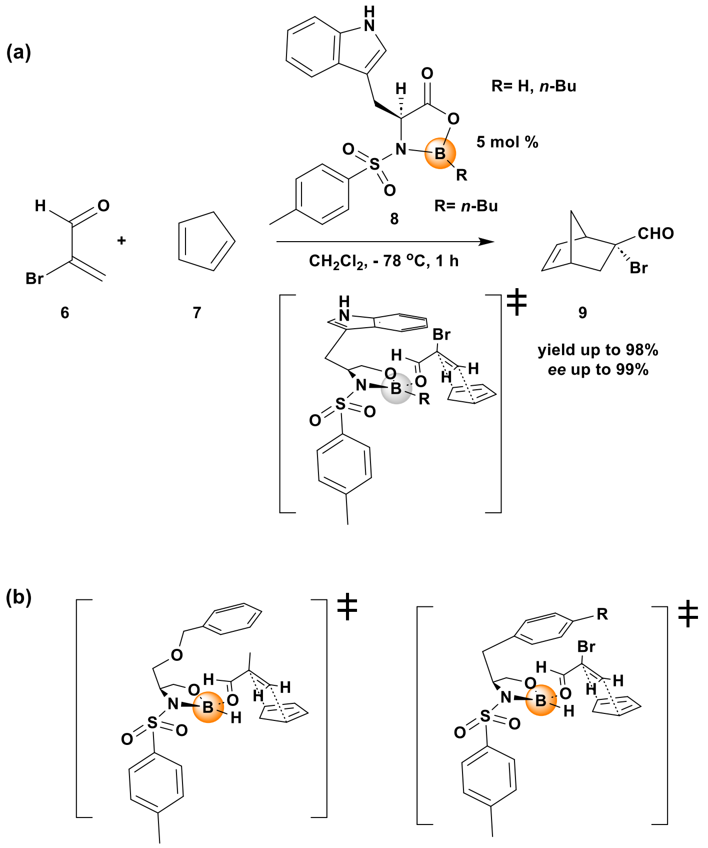
3.1. Diels–Alder reaction

For about a century, the classical organic Diels–Alder reaction has been a reliable method to synthesize substituted cyclohexenes. This includes the [4 + 2] cycloaddition between a conjugated diene and dienophile. The mechanism is based on frontier molecular orbital interactions, which were introduced by Otto Diels and Kurt Alder in 1928.[25,26] To achieve stereocontrol in asymmetric Diels–Alder reactions, chemists often depend on chiral auxiliaries or chiral Lewis acids to obtain both diastereo- and enantioselectivity.

In this regard, catalytic metal centers are used to coordinate with chiral amino acid ligands to form metal–amino acid complexes. These chiral ligands promote the catalysts to create a chiral environment that alters diene and dienophile alignment in the transition state. Changing the metal spatial arrangement with a chiral amino acid could manipulate the enantiomeric outcomes.

One of the very first examples, Helmchen and colleagues highlighted the successful catalysis of enantioselective Diels-Alder reactions of enals by employing chiral Lewis acids derived from N-sulphonylamino acids coordinating with borane metal center [Figure 1. (a)].[18] Diels–Alder reaction between 2-bromoacrolein (**6**) and cyclopentadiene (**7**) using a chiral oxazaborolidine catalyst (**8**), affording the exo adduct (**9**). However, their research not only gravitates around finding optimal amino acid counterparts, along with the study also emphasizes the crucial importance of donor solvents in achieving optimal enantioselectivity. This resulted in the most favorable outcomes of 86% of enantiomeric excess (*ee*) when DCM/THF was used as solvent. They rationalized that steric and electronic effects of catalyst substituent and boron coordination site control the enal conformation and chirality, which leads to a transition state favoring diene attack from the Cα-*Si* enal face. The concept of “species multiplicity” is introduced, linking enantioselectivity to catalyst purity, concentration, substrate structure, and solvent effects. This work underscored the complexity of these systems and the need for precise tuning to achieve optimal selectivity. They established an early model for understanding ligand–metal–solvent interplay in asymmetric catalysis.

Around the same time, Corey *et al.* presented a similar strategy by leveraging advantageous intramolecular interactions and classical steric effects.[27] Novel (*S*)-tryptophan-derived oxazaborolidine catalyst showcased exceptional enantioselectivity and diastereoselectivity [Scheme 1. (a)]. In continuation, the study of asymmetric Diels-Alder reactions, catalyzed by chiral oxazaborolidines from amino acids, revealed how electron-donor functionality impacts enantioselectivity.[11] The research revealed that the presence of electron-donor atoms at specific positions of the aromatic side chain of amino acids has a significant impact on enantioselectivity of the reaction by creating a favorable orientation of the transition state [Scheme 1. (b)]. The strategic positioning of the moiety allows for optimal donor-acceptor interactions between substrate and catalyst, playing a significant role in controlling the stereochemistry of the resulting product.



Scheme 1. (a) E. J. Corey's borane-amino acid complexes catalyzed Diels–Alder product, and (b) aromatic ring influenced favorable orientation of the transition state.

Along with these pioneering works, Engberts and co-worker demonstrated a groundbreaking discovery in the same field, revealing the significant impact of water on the enantioselectivity in a chiral Lewis-acid catalyzed Diels–Alder reaction.[28,29] A comprehensive analysis of ligands has uncovered that copper coordinated specific aromatic amino acids play a crucial role in enhancing enantioselectivity through π–π interactions between aromatic rings of ligand and substrate in favorable transition state. The chiral Cu–amino acid complex activates the dienophile in water, where arene–arene interactions in the transition state boost enantioselectivity to give high *ee* [Figure 2]. These discoveries establish the understanding of amino acid-derived chiral ligands and their effects in aqueous Lewis acid catalysis.

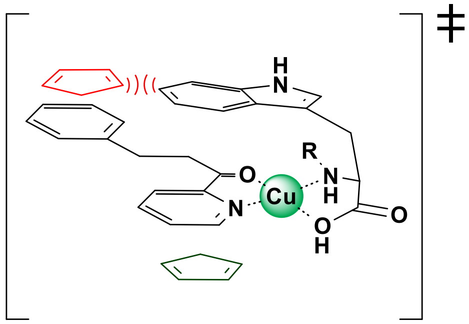
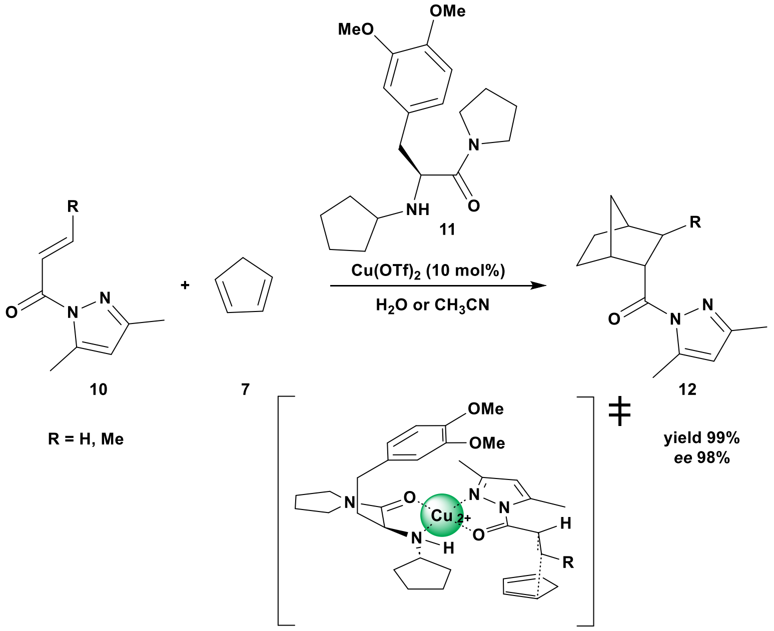


Figure 2. Transition state of Cu-amino acid catalyzed Diels–Alder reaction showcased steric hindrance.

Owing to its well-understood mechanism, Ishihara and co-workers showcased the rational design of minimal artificial catalysts for the asymmetric Diels–Alder reaction, utilizing copper cation–π interactions [Scheme 2].[30,31] They demonstrated that their catalyst effectively transformed α,β-unsaturated 1-acyl-3,5-dimethylpyrazoles (**10**) and cyclopentadiene (**7**) into the corresponding Diels–Alder adducts (**12**) in quantitative yield. Through the utilization of L-DOPA (3,4-dihydroxyphenylalanine)-derived monopeptides (**11**) as ligands, these catalysts demonstrated their ability to efficiently facilitate enantioselective (as high as 98% *ee*) in asymmetric Diels-Alder reactions. This approach highlights the cost-effective and adjustable properties of monopeptides, providing a promising alternative to more intricate ligands.



Scheme 2. Amino acid–copper complex catalyzed asymmetric Diels–Alder reaction involving cation–π interactions in the transition state.

Following this work, Furutani's C_2-symmetric diketopiperazine from cyclo[-His-His-] when complexed with $Cu(OTf)_2$ successfully catalyzed asymmetric Diels–Alder reactions with moderate enantioselectivity (up to 35% *ee*) and high yields (up to 76%). [32] They disclosed that trityl groups on the peptide ligand are responsible for the stereoselectivity of the reactions, emphasizing the need for a strict chiral environment surrounding the metal center.

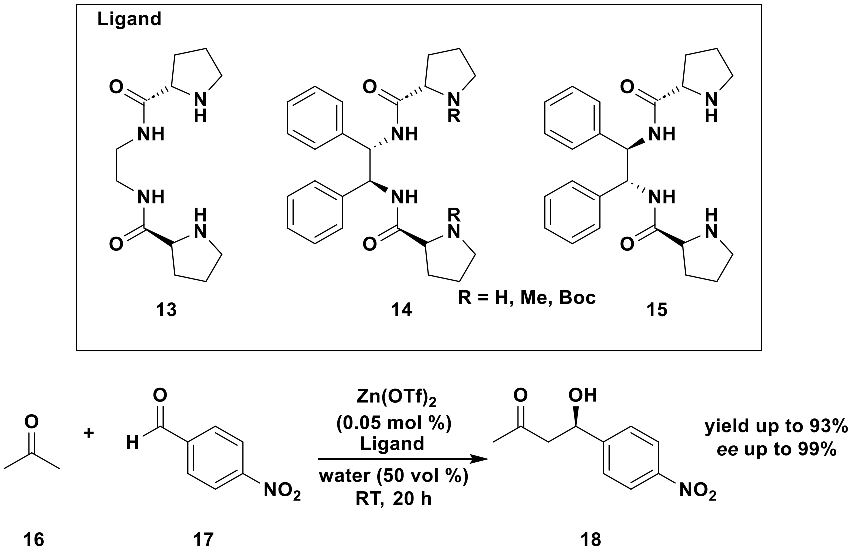
3.2. Aldol reaction

In 1872, Wurtz first reported the aldol reaction, a fundamental process in nature as well as in synthetic laboratories. The aldol reaction facilitates the formation of β-hydroxyketones, with a maximum of two newly formed stereocenters. This reaction is essential to produce complex chemical structures. However, it is difficult to achieve a high degree of selectivity in terms of chemical, positional, and stereochemical outcomes. To address the problem, researchers thought to mimic nature's aldolase enzymes.[33]

A century after the discovery of the aldol reaction, Zn–amino acid ester complex was introduced as a potential catalyst for asymmetric aldol reactions.**[34]** The work shows that Zn complexes of α-amino acid esters efficiently catalyse aldol condensations of *p*-nitrobenzaldehyde with acetone under gentle, neutral conditions. The catalytic activity and enantiomeric excess were dramatically increased in complexes with ligands containing benzene rings, such as esters of phenylalanine, tyrosine, and tryptophan. These outcomes concluded that the steric effects of the chiral ligands are significant in both reactivity and asymmetric induction.

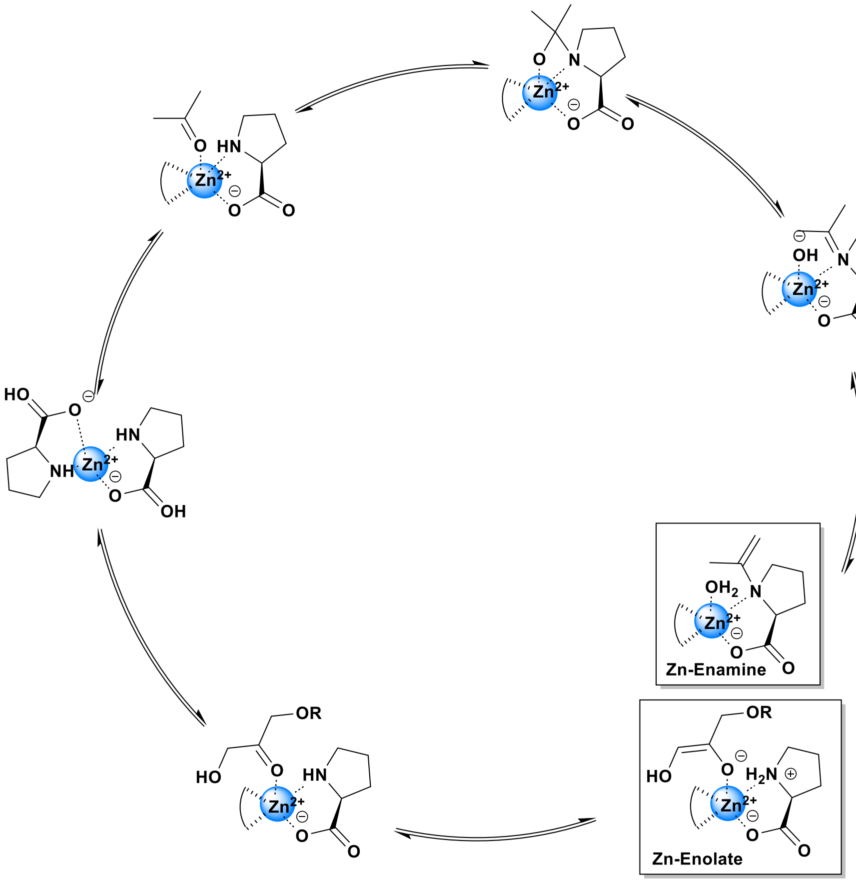
In extension of the findings, the Zn–(proline)$_2$ complex efficiently facilitated direct asymmetric aldol reactions in aqueous media, exhibiting excellent yield and selectivity with different aromatic aldehydes.[35,36]The catalyst functioned at ambient temperature and achieved up to 56% *ee*. The study shows that zinc acts as a Lewis acid to form the enolate, while the proline ligand drives the desired stereoselectivity through a favourable transition state. This greener approach showed that metal–amino acid complexes can facilitate aldol reactions in an eco-friendlier way without organic solvents.

Following this green approach, Paradowska *et al.* demonstrated that their C$_2$-symmetric bis-prolinamide (**13**-**15**)–zinc catalyst afforded up to 98% ee of aldol adduct (**18**) in the aqueous aldol reaction between acetone (**16**) and 4-nitrobenzaldehyde (**17**) [Scheme 3].[12] The reaction exhibits a high level of efficiency, as even a small catalytic load of 0.5 mol% produced noteworthy outcomes. The process is ecologically sustainable, as it does not need the use of organic solvents like previous works. It achieves exceptional control over the arrangement of atoms in a molecule, especially when cyclohexanone is used as the starting material. Furthermore, the researchers explored the potential of Sc(OTf)$_3$ and Yb(OTf)$_3$ as metal additives alongside a bis-prolinamide ligand. They reported a highly impressive outcome with up to 99% *ee* by accurately replicating the natural aldolase enzymes.



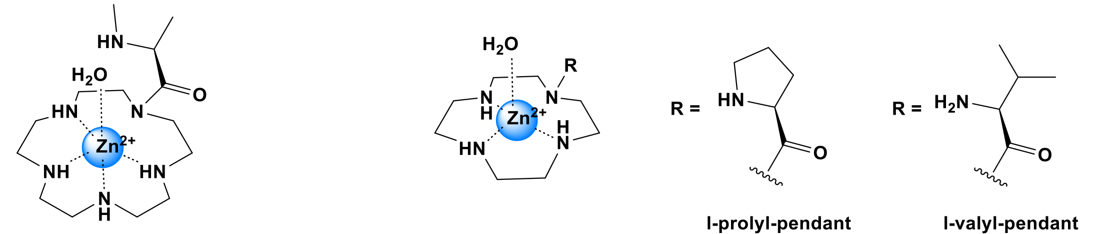
Scheme 3. Asymmetric aldol reaction catalyzed by a zinc triflate complex with a *C*$_2$-symmetric chiral bis-prolinamide ligand (**13**-**15**).

In continuation of this path, zinc–proline complex catalyzed aldol reactions exhibit a dual mechanism in aqueous media, analogous to type I and type II aldolases.[37] Reymond and colleagues showed that the reaction pathway depends on the substrate: for acetone, it followed an enamine mechanism (type I aldolases), as indicated by the reductive trapping of the iminium intermediate. On the other hand, dihydroxyacetone underwent an enolate mechanism (type II aldolases), with the deprotonation of the α-carbon being the rate-limiting step. The mechanistic switch in this process is affected by the hydroxyl groups present in the substrate [Scheme 4]. These functional groups lower the pKa and provide stability to the intermediate, enolate, showcasing the remarkable catalytic capabilities of the zinc–proline catalytic complex in efficiently facilitating both enamine and enolate pathways. Nevertheless, they do not provide significant insight into the stereoselectivity of the zinc–proline complex-catalyzed aldol reactions.



Scheme 4. Mechanistic pathway of zinc–proline catalysis.

Following the path of chiral amino acid and Zn complex-mediated aldolase mimic, Itoh *et al.* investigated the mechanistic approach of synthetic aldolase.[19] The group synthesized and characterized Zn complexes of l-prolyl-pendant [15]aneN_5 (**19**), l-prolyl-pendant [12]aneN_4 (**20**), and l-valyl-pendant [12]aneN_4 (**2**) for use as chiral catalysts in enantioselective aldol reactions [Figure 1. (b) & Figure 3]. The results of the potentiometric titrations indicated that l-prolyl-pendant [15]aneN_5-Zn complex exhibited the highest level of stability among the complexes, with a logK value of 14.1. In contrast, the other two complexes demonstrated increased Lewis acidity, which enhanced their catalytic efficiency. The aldol reactions catalyzed by l-valyl-pendant [12]aneN4-Zn complex resulted in up to 89% *ee* and exceeding 70% yields. This high enantioselectivity can be attributed to the synthesis of Zn-enolates rather than Schiff bases.


l-prolyl-pendant [15]aneN_5–Zn complex

19

l-prolyl-pendant [12]aneN_4–Zn complex

20

l-valyl-pendant [12]aneN_4–Zn complex

2

Figure 3. Zn complexes of l-prolyl-pendant [15]aneN_5 (**19**), l-prolyl-pendant [12]aneN_4 (**20**), and l-valyl-pendant [12]aneN_4 (**2**).

In 2011, Penhoat *et al.* highlighted the remarkable improvement in the stereoselectivity of the direct asymmetric aldol reaction when group 12 element chloride salts, specifically $ZnCl_2$, are combined with L-proline in water.[38] Under the carefully designed conditions [L-proline 20% and $ZnCl_2$ 10% in a DMSO/H2O (80:20) solvent mixture], the aldol product (*anti*) displays an exceptional enantioselectivity of over 99% *ee*. L-proline catalyzes the reaction by forming an enamine intermediate with the ketone. Followed by, this enamine attacks the aldehyde, leading to C–C bond formation with stereocontrol.

Shifting focus to copper-based systems, Hong Wang and research group effectively crafted a family of Cu–amino acid (**21**-**24**) complexes containing primary amine moieties for asymmetric direct aldol reactions [Figure 4].[39,40] The ligands, synthesized from primary amino acids, delivered high reactivity and excellent stereoselectivity (up to 99% ee) with $Cu(SbF_6)_2$. These catalysts operated efficiently across various cyclic ketones and aldehydes. Their performance arizes from a cooperative mechanism involving enamine formation and Lewis acid activation, enabling reactions under mild, air- and water-tolerant conditions. This dual activation strategy resembles the Type I aldolase, where a lysine residue forms an enamine with the donor ketone. The tunability of both the metal center and amino acid framework further underscores the adaptability of these catalysts for broader asymmetric applications.

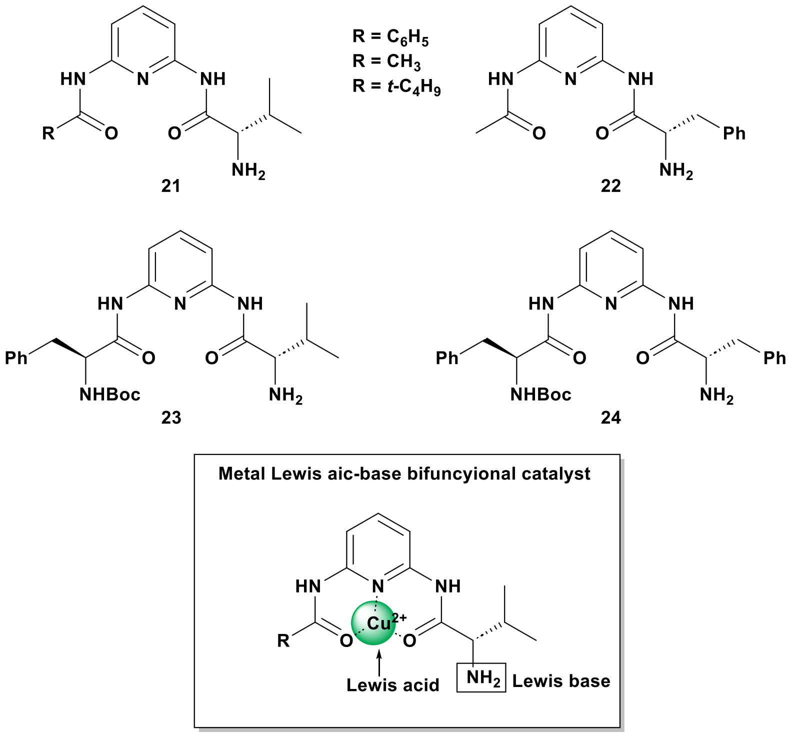


Figure 4. Amino acid-derived ligands and their Cu complex.

Further progress was reported by Mlynarski and co-workers, who effectively created a range of Yb complexes using C_2-symmetry chiral ligands obtained from amino acids. These ligands are covalently attached to a chiral backbone, such as (*S*,*S*)-hydrobenzoin or (*S*,*S*)-diphenylethylenediamine, and C_2-symmetricity ensures a well-defined and rigid chiral environment for coordination. These metal–ligand complexes were shown to be useful in facilitating asymmetric aldol reactions.[41] Modifying the amino acid residues (e.g., methylated, N-ethyl, N-benzyl) enabled fine-tuning of steric and electronic effects around the Yb center. A maximum 64% *ee* was obtained by employing ligands that had aromatic backbones and N-alkyl groups in combination with $Yb(OTf)_3$. Less electrophilic anisaldehydes gave lower yields but improved enantioselectivity.

NMR studies confirmed Yb coordination to the C_2-symmetric framework, clarifying key metal–ligand interactions. These results highlight the potential of amino acid-derived ligands in lanthanide-based asymmetric aldol catalysis.

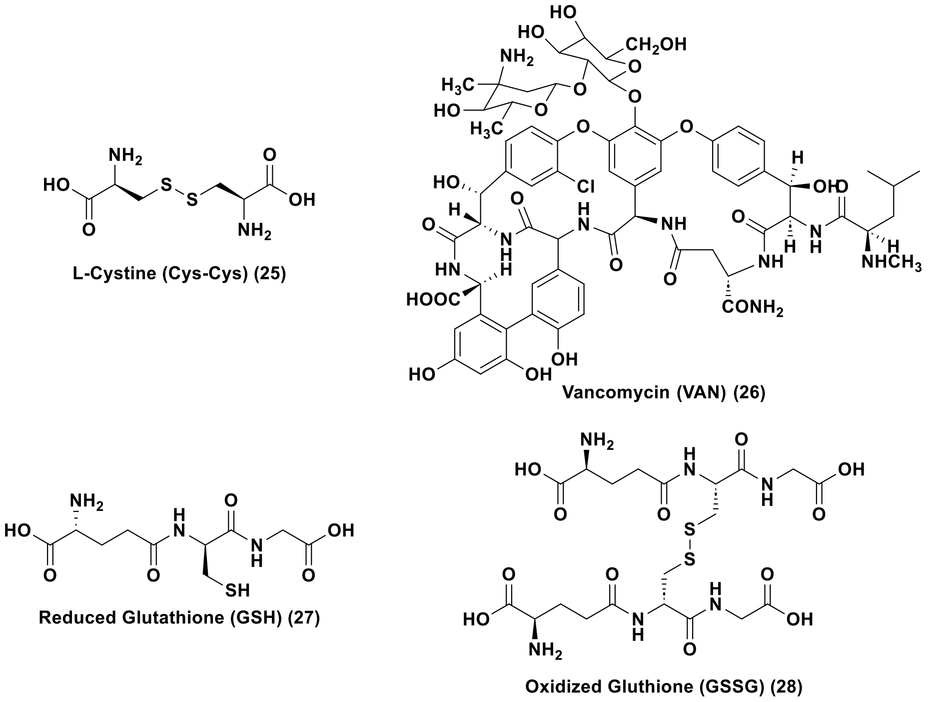
In a recent study, tuning the pore size of Zr-MOFs allows proline and thiourea units to work in a confined chiral space.[42] This boosted aldol reaction outcomes with 83% yield and *ee* up to 73%. Here, the amino acid acts as both the catalytic engine as well as the stereochemical guide.

3.3. Conjugate addition reactions

Conjugate addition reaction is an indispensable process in organic chemistry, frequently facilitated by transition metals as catalysts. The study of these reactions has received significant attention, particularly in the field of asymmetric reactions, where chiral ligands are of utmost importance.[43]

Herrmann and colleagues demonstrated the production of phosphorous-functionalized trimeric amino acid ligands for conjugate addition reaction.[44] This was achieved by reacting tris(hydroxymethyl)phosphine with an excess of amino acids in water using a Mannich-type condensation process. The ligand's catalytic potential in propylene hydroformylation was investigated in this work by coordinating with rhodium metal. The selectivity observed with these ligand systems can be easily tuned by adjusting the pH of the reaction mixture. However, no comment was made regarding the asymmetry of the products.

Following the same trajectory, oligopeptide-rhodium complexes were employed for the hydroformylation of styrene in a biphasic medium.[13] The results showed that ligands with thiol groups, such as L-cysteine (**25**) and reduced glutathione (**27**), stabilize catalytic activity, allowing numerous recyclings with constant performance [Figure 5]. Ligands without thiol groups, such as L-tryptophan and L-methionine, leach metal, making them unsuitable for recycling. Although enantioselectivity was not observed, these outcomes highlighted the role of amino acid-derived ligands to provide stability in addition reactions.



L-Cystine (Cys-Cys) (25)

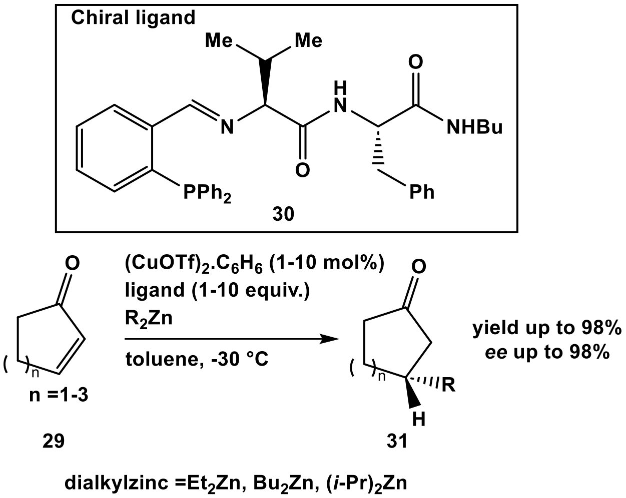
Vancomycin (VAN) (26)

Reduced Glutathione (GSH) (27)

Oxidized Gluthione (GSSG) (28)

Figure 5. Oligopeptide ligand (**25**-**28**) structures for the hydroformylation of styrene.

Degrado *et al.* showcased that the use of modular peptide-based phosphine ligands (**30**) in conjunction with CuOTf as a metal precursor effectively catalyzes enantioselective conjugate additions. In this study, they worked with dialkylzinc reagents and five-, six-, and seven-membered cyclic enones (**29**) [Scheme 5]. [45,46] These results showcased high enantioselectivities over 98% *ee*, along with good yields of addition products (**31**). The optimisation of ligand structure improves the enantioselectivity for sterically hindered substrates, making this technique very adaptable for asymmetric addition reactions.



Scheme 5. Enantioselective addition to cyclopentenones.

Following the path, the asymmetric addition of dialkyl- and diarylzinc reagents to acyclic β-silyl-α,β-unsaturated ketones is reported.[47] The reactions were catalyzed by a valine-based chiral phosphine ligand in coordination with copper, resulting in the formation of allylsilanes with excellent diastereo- and enantiomeric purity. The approach attains yields ranging from 59% to 96% with enantiomeric excesses up to 96%. The valine ligand's steric configuration directs nucleophilic attack to one face of the β-silyl enone, enabling highly selective 1,4-addition. This flexible, straightforward approach expanded the scope of ACA reactions to previously challenging diarylzinc substrates.

Breit and co-worker demonstrated that their copper–peptidyl phosphane ligand (**32**-**38**) complexes allow feasible addition of dialkylzinc reagents to cyclic enones with exceptional enantioselectivity, crossing over 97% *ee*.[48] The design of the ligand is very important for this efficiency, and the choice of amino acids and how they are arranged has a big effect on the stereochemical result [Figure 6]. These amino acids, with their chiral centers and sterically demanding side chains, help orient the substrate and dialkylzinc nucleophile in transition states. The modular structure of these ligands, especially their non-covalent interactions, makes them a flexible base for asymmetric catalysis.

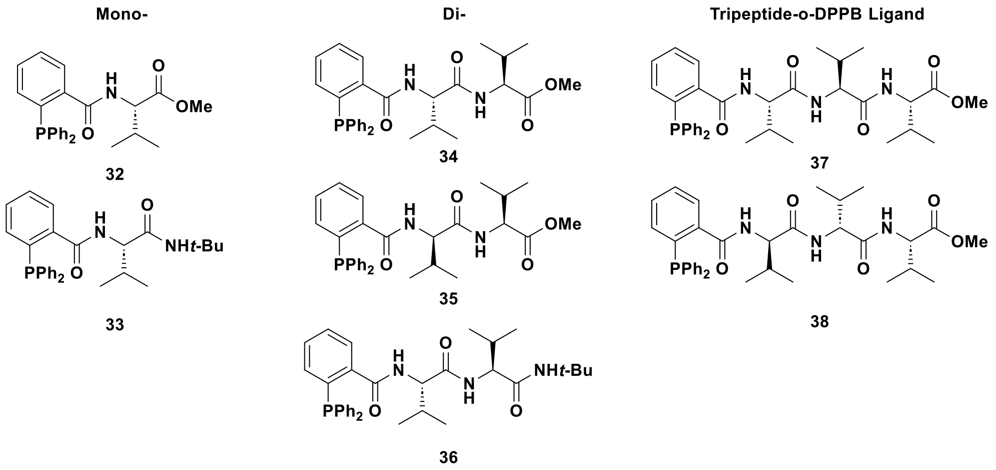
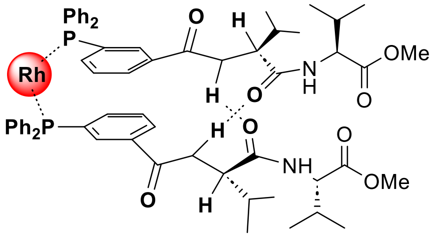


Figure 6. Structures of peptidyl phosphane ligands (**32**-**36**).

In 2008, the same research team developed novel phosphorus ligands derived from amino acids.[49,50] These ligands self-assembled through hydrogen bonding and worked effectively in rhodium-catalyzed asymmetric hydrogenation and getting up to 99% *ee*. Because of their strong hydrogen-bonding interactions and helix secondary structures, these Rh–peptide complex (**39**) has an extensive range of catalytic activity and enantioselectivity [Figure 7]. These cooperative hydrogen-bonding interactions between ligands not only defined the chiral environment but also expanded the catalytic scope across a variety of substrates.



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"SupraPhanePhos"
central to planar chirality
induced through self-assembly

Figure 7. Schematic representation of hydrogen-bonding interactions derived helix secondary structures.

Arya *et al.* described the possibility of making complex branching amino acid phosphonated ligands, which were fixed on solid-phase beads [Figure 8].[51] This was done by putting them together one step at a time, which led to Rh-based catalyst (**40**) in the final step by reacting with $Rh(CO)_2Cl_2$. These catalysts showed high reactivity and selectivity in hydroformylation reactions, where products are inclined towards a branching structure instead of a linear structure. Although the study did not address enantioselectivity, it demonstrated the potential of solid-supported, amino acid-based architecture for flexible, recyclable catalyst design.

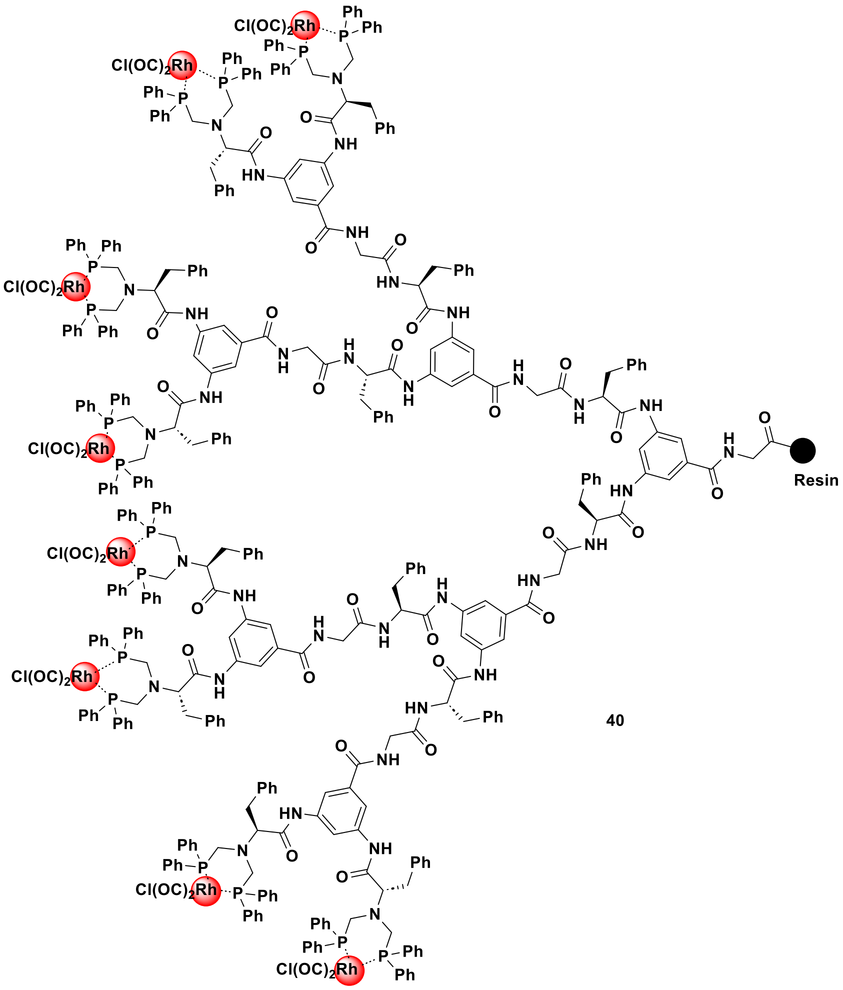
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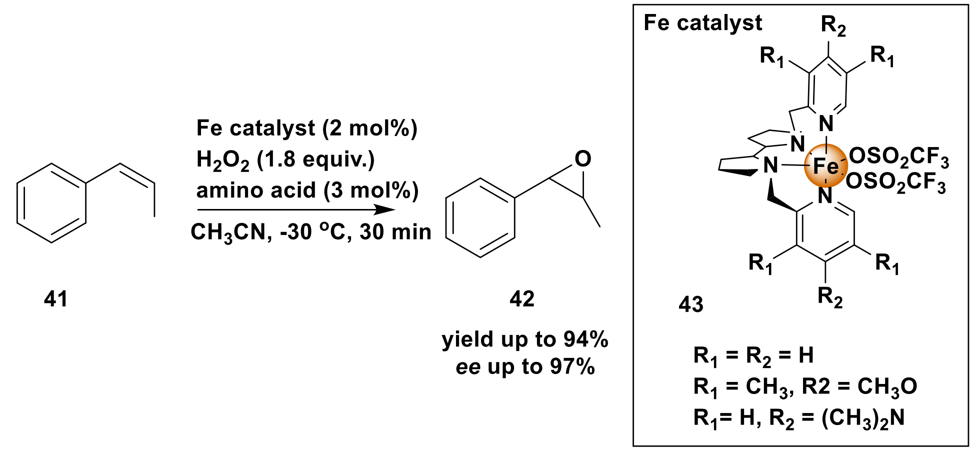
Figure 8. Octavalent dendritic ligand–Rh complex (**40**).

3.4. Oxidation

3.4.1. Epoxide synthesis. Chiral oxidations are significant to produce enantioselective epoxides, which are important intermediates in organic synthesis as well as natural product research. Advancements in bioinspired catalysts, such as iron-porphyrin and non-heme systems, efficiently catalyze asymmetric epoxidation reactions using hydrogen peroxide.[52]

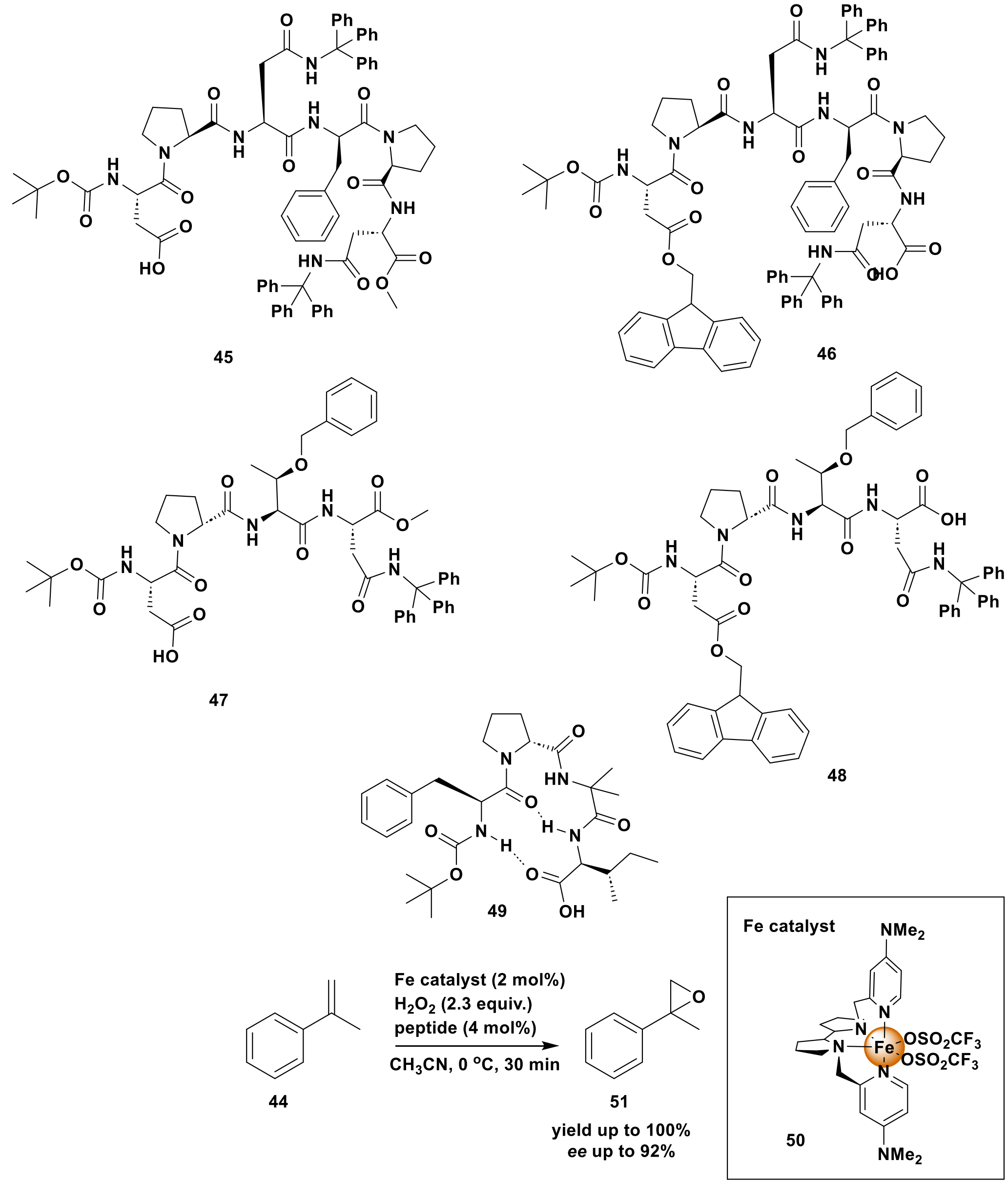
Along with that, incorporating amino acids into these systems enhances enantioselectivity by creating second coordination-sphere effects, thereby refining substrate recognition and transition-state stabilization. Vaibhav *et al.* first reported an amino acid-derived chiral immobilized oxidation catalyst. They used L-valine as an amino acid sourced in polymer support to coordinate with ruthenium, providing moderate olefin epoxidation catalysts.[53] The catalytic epoxidation of styrene, norbornylene, cyclooctene, and cyclohexene was studied utilizing immobilized catalysts with *tert*-butyl hydroperoxide (*t*-BuOOH) as the terminal oxidant. Although activity and recyclability were moderate, applicability was limited, and enantioselectivity was not reported.

In 2015, Costas and his research group described a way to do highly enantioselective epoxidation of α-alkyl-substituted styrenes (**41**). They used a bioinspired non-heme iron catalyst (**43**) and N-protected amino acids as co-ligands [Scheme 6].[54] The synergistic effect of the iron center and amino acids allows for effective activation of H_2O_2, resulting in high enantioselectivities product (**42**) (up to 97% *ee*). This technique employs environmentally benign iron and aqueous H_2O_2 and enables accurate control of stereochemistry by carefully choosing desired amino acid ligands. Out of all the N-protected amino acids that were studied, N-Boc-*t*-Leu-OH emerged as the optimal co-ligand for achieving the maximum enantioselectivity and yield. The amino acid carboxylate coordinates the metal, tuning the electrophilicity of the iron-oxo species to make it reactive and selective toward the alkene.



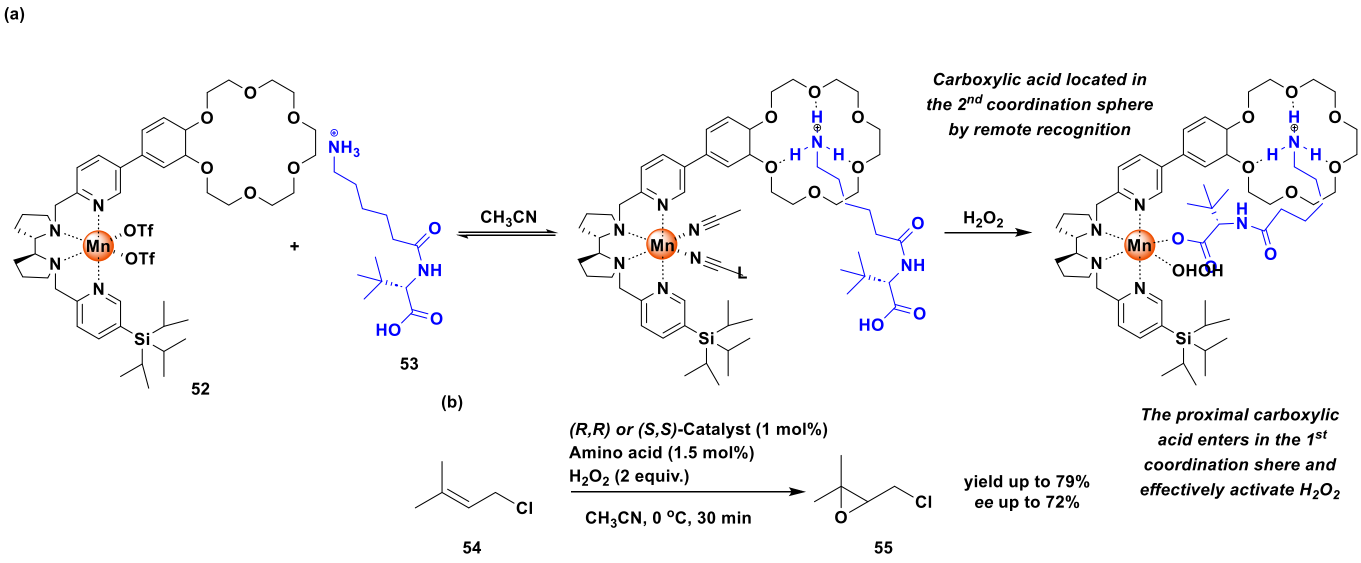
Scheme 6. Asymmetric epoxidation by utilizing Fe–amino acid complex.

Building upon previous research, the group has developed a highly selective and efficient catalytic system for asymmetric epoxidation on prop-1-en-2-ylbenzene (**44**) to produce 2-methyl-2-phenyloxirane (**51**).This transformation achieved utilizing a peptide (**45**-**49**) and its supramolecular interactions along with Fe catalyst (**50**) [Scheme 7].[55] This work emphasized the importance of the peptide's β-turn structure in producing significant enantioselectivity when combined with iron as a metal center. The catalytic system that has been created demonstrates excellent yields with as high as 92% *ee* under gentle conditions. The system exemplified how peptide secondary structure can manifest enzyme-like pockets that regulate the stereoselectivity in oxidation reactions.



Scheme 7. Asymmetric epoxidation by utilizing Fe–peptide complex.

In recent years, Costas and colleagues came up with a novel supramolecular approach for activating hydrogen peroxide by using a manganese oxidation catalyst (**52**), which resembles the metalloenzymes.[14] The researchers successfully performed catalytic asymmetric epoxidation on 1-chloro-3-methylbut-2-ene (**54**) to yield product **55** using a distant amino acid (**53**) that binds by ammonium-crown ether recognition [Scheme 8]. This approach dramatically reduced the required carboxylic acid loading and underscored the importance of precise spatial organization in reproducing enzyme-like selectivity.



Carboxylic acid located in the 2nd coordination sphere by remote recognition

The proximal carboxylic acid enters in the 1st coordination shere and effectively activate H2O2

(R,R) or (S,S)-Catalyst (1 mol%)
Amino acid (1.5 mol%)
H_2O_2 (2 equiv.)
CH_3CN, 0 °C, 30 min

yield up to 79%
ee up to 72%

Scheme 8. (a) a remote amino acid (**53**), anchored through ammonium–crown ether recognition, (b) catalytic asymmetric epoxidation employing H_2O_2 activation.

3.4.2. Water oxidation. Water splitting is one of the cornerstone techniques for producing hydrogen as a sustainable energy source. The initial and most difficult phase in this process is water oxidation. This is hard to achieve as it is hindered by slow kinetics and the need to perform several bond rearrangements. Water oxidation requires the use of efficient catalysts to decrease the energy barriers. The oxygen-evolving complex in photosystem II (OEC-PSII) found in nature serves as a source of inspiration for the development of water oxidation catalysts (WOCs). Specifically, there is interest in creating WOCs that use earth-abundant metals such as copper and cobalt due to their improved stability.[56,57]

A novel copper–peptide complex (**56**) was introduced, which has proven to be a highly effective electrocatalyst for water oxidation at low overpotential [Figure 9].[16] These Cu–peptide complexes, which draw inspiration from nature, demonstrate an impressive faradaic efficiency of up to 91% with an overpotential up to 800 mV. The peptides of the complexes form a stable intramolecular complex that remains active, resembling enzymatic second coordination spheres. The ethanolic side chain of the peptides is a cornerstone for maintaining the stability and activity of the catalytic complex. Those hydroxyl groups help in binding water and facilitating proton shuttling, which is essential for the water oxidation process.

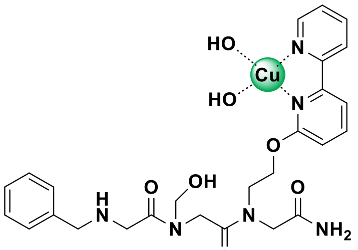


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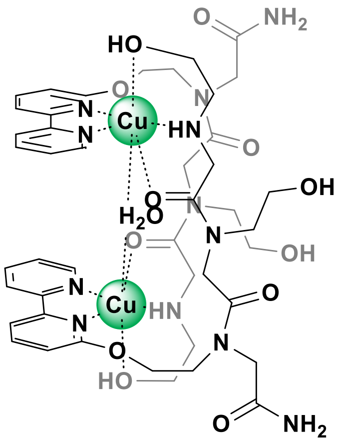
Figure 9. Structure of Cu–peptide complex (**56**) for water oxidation.

Following the same trajectory of the research, Galia Maayan and colleagues introduced a novel dicopper–peptide duplex (**57**) as a very effective electrocatalyst for the process of water oxidation [Figure

10].[58] The ligand is a peptide trimer that consists of one 2,2′-bipyridine ligand and two ethanolic groups, readily synthesized on a solid support. The peptide scaffold enhances the stability of copper ions in a high-oxidation state and helps to improve the efficiency of the catalytic process. The catalyst works at pH 9.35 with a low overpotential of 450 mV and has a high turnover frequency (TOF) of up to 5503 s^{-1}, which is the highest of any Cu-based electrocatalyst. The characterization shows that ethanolic side chains and borate buffer enhance the complex's stability and activity. The peptide coordinates copper and enables Proton-Coupled Electron Transfer (PCET), which is essential for hydrogen generation.

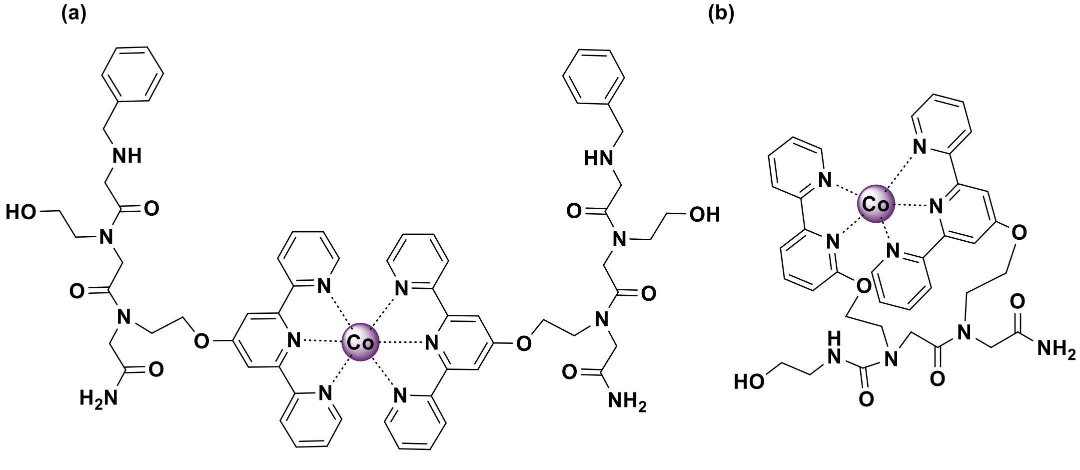


57

Figure 10. Structure of dicopper–peptide duplex (**57**).

After achieving desired catalysis with copper–peptide complexes, a cobalt–peptide complex (**58**) was made, a rapid and effective electrocatalyst for homogenous water oxidation.[59] The peptide trimer of the catalyst has a terpyridine and an ethanol group, stabilizing the cobalt center [Figure 11 (a)]. This allows water to bind more easily and facilitate oxidation, with a low overpotential of 350 mV and a fast reaction rate of 108 s^{-1}. The electrocatalytic activity is due to the special coordination environment created by the peptide scaffold, which mimics the enzyme activity and keeps the Co center stable during the catalytic process.

Following the research, an intramolecular cobalt-peptide complex (**59**) was introduced, which can help break down water more efficiently.[60] In contrast to the previous research, this bio-inspired Co complex has a peptide ligand with terpyridine and bipyridine anchors [Figure 11 (b)]. The catalyst showcased a high stability and a low overpotential of about 430 mV. The ethanolic side chain of the peptide and bipyridine ligand is very important for keeping the catalyst stable and acting like an enzyme. This is creating a benchmark towards making effective water oxidation catalysts out of non-precious metals.



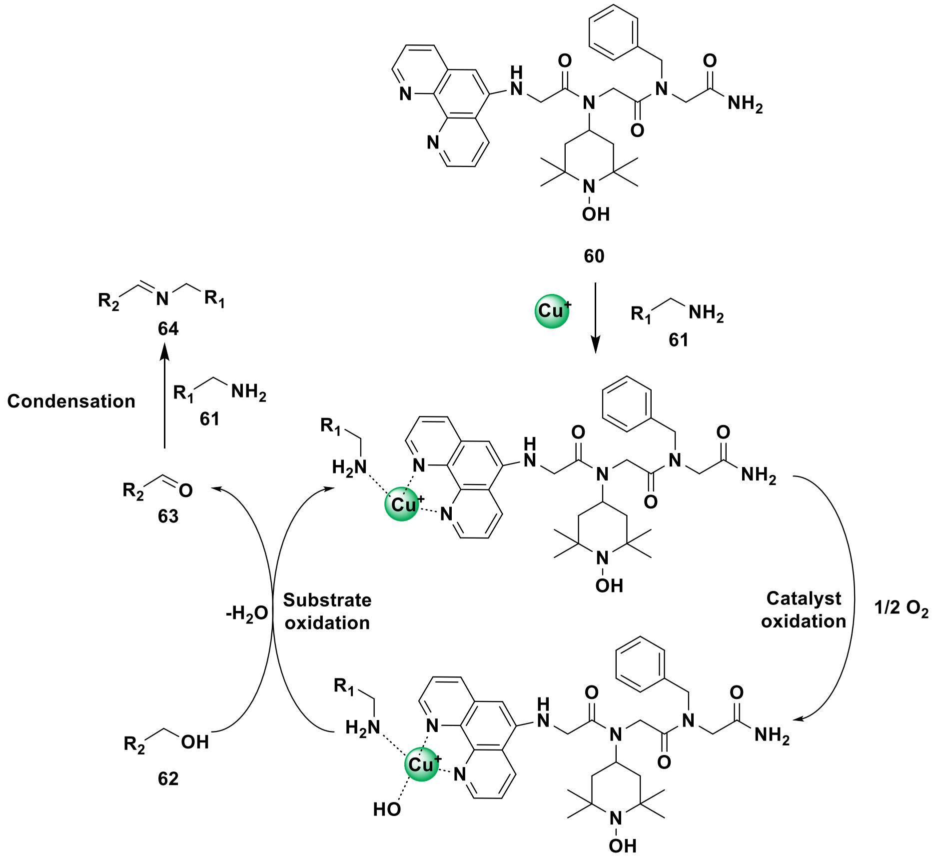
58 **59**

Figure 11. Cobalt–peptide complexes for water breakdown: (a) intermolecular cobalt-peptide complex (**58**), (b) intramolecular cobalt–peptide complex (**59**).

3.4.3. Other oxidations. Maayan and co-workers have made substantial contributions to the investigation of biomimetic catalysts in many oxidation processes, in addition to water oxidation. The researchers demonstrated the oxidation of primary alcohols using a metallo–peptide catalyst that employs phenanthroline–copper, (2,2,6,6-tetramethyl-1-piperidinyl)oxydanyl (TEMPO), and a peptide backbone.[61] The metal catalysts exhibited much greater turnover numbers (TON) up to 16-fold compared to randomly placed catalytic groups or peptide dimers without a non-catalytic group. The work highlighted the significance of positioning catalytic groups in proximity on the peptide scaffold to achieve optimal catalytic activity. Remarkably, they observed that including non-catalytic groups significantly increased catalytic activity by facilitating the creation of a more effective intramolecular catalytic pocket.

In a follow-up work, researchers have created a metallo–peptide trimer (**60**) that consisted of phenanthroline–copper and TEMPO as a catalytic center.[62] This amino acid-derived trimer has demonstrated highly effective towards intramolecular cooperative catalysis for the aerobic oxidative production of imines (**64**) from amine (**61**) and alcohol (**62**) [Scheme 9]. This biomimetic catalyst demonstrated a substantially greater TON. The work showcased the efficacy of metallo–peptide trimer in generating diverse imines from alcohols and amines, exhibiting good selectivity and conversions. This makes it a desirable tool for synthesizing intermediates in the production of novel chemicals and active pharmaceutical ingredients (APIs).

Followed by, Maayan and the research group shifted their focus to solid-grafted metallopeptide catalysts, aiming to develop a reusable biomimetic catalyst. Researchers produced resin-bound peptide trimer and dimer compounds that serve as reusable heterogeneous catalysts for oxidation reactions. This biomimetic catalyst specifically targets the oxidation of primary alcohols and the oxidative coupling of alcohols and amines.[63] They discovered that the resin-bound peptide dimer had more catalytic activity in comparison to both the resin-bound peptide trimer and its soluble versions. This is likely due to the collaborative interactions taking place inside and between the resin. The peptide dimer catalyst could be reused, reaching a TON of 296 over several cycles.



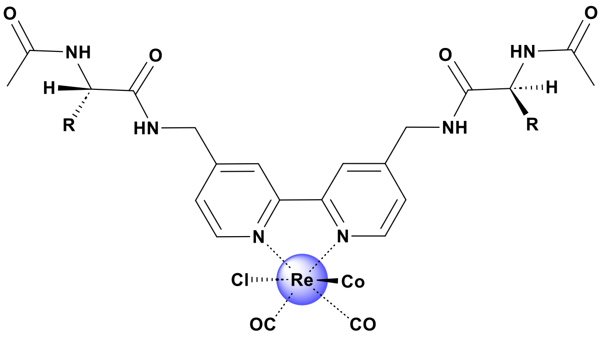
Scheme 9. Proposed mechanism for imine (**64**) synthesis with Cu–peptide complex.

Scientists have crafted a novel MOF that acts as a supramolecular catalyst, imitating the activity of catechol oxidase.[64] This framework is formed by the self-assembly of nucleotides (guanosine monophosphate), Fmoc-modified amino acids (Fmoc-Lysine), and copper. This catalyst demonstrated improved catalytic efficiency and durability in aqueous environments, while maintaining its effectiveness up to a temperature of 95 °C. The assemblies of amino acids and copper, helped by fluorenyl stacking, play a vital role in the formation of active copper clusters. This provides valuable knowledge for the development of bioinspired catalysts with a supramolecular approach.

3.5. Reduction

3.5.1. Carbon dioxide (CO_2) reduction In the fight against climate change and for the long-term viability of energy sources, the chemical process of CO_2 reduction has paramount importance. The technique can help lower greenhouse gases in the atmosphere by converting CO_2 into less toxic products. However, in order to reduce CO_2 efficiently, specialized electrocatalysts are needed, which can catalyze the process selectively and effectively even under moderate circumstances.[65]

Amino acid ligands could be crucial for optimizing the performance of these electrocatalysts. In 2016, Machan *et al.* introduced new rhenium-based bimetallic supramolecular electrocatalysts (**65**) containing either phenylalanine or tyrosine residues, as depicted in Figure 12.[17] The use of Spectro-electrochemical research and computational modelling revealed that tyrosine residues play a crucial role in augmenting catalytic activity by serving as proton donors and providing structural stability to the catalyst. The tyrosine-based complex outperformed the phenylalanine-based catalyst in converting CO_2 to CO and CO_3^{2-}. The results showcased that non-covalent assembly is a viable approach for creating novel amino acid-derived electrocatalysts with adjustable topologies and functions, which leads to enhanced catalytic efficiency.



65

a: R = -$CH_2PhOtBu$; Re(Tyrdac)$(CO)_3Cl$
b: R = -CH_2Ph; Re(Phedac)$(CO)_3Cl$

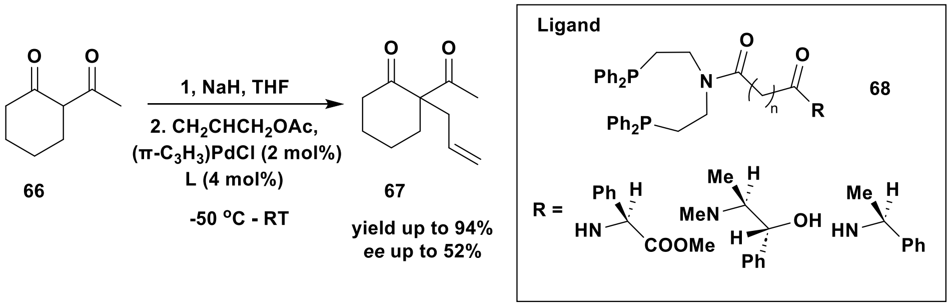
Figure 12. Rhenium-based bimetallic supramolecular electrocatalysts (**65**).

3.5.2. Ketone reductions. One of the most significant methods to produce chiral secondary alcohols is the extremely enantioselective reduction of ketones utilizing an easily accessible metal–ligand complex.[66] This process is useful for both small-scale laboratory applications and large-scale commercial applications.

Adolfsson and co-workers introduced a remarkably precise method for reducing aryl, alkyl ketones to secondary alcohols.[67-69] The process utilizes ruthenium catalysts in combination with innovative pseudo-dipeptide ligands, resulting in high enantioselectivity. The ligands, synthesized from L-N-Boc-protected α-amino acids and (*S*)-amino alcohols, led to catalysts that achieved an impressive 98% *ee* in asymmetric ketone reduction. The reduction was carried out using hydrogen-transfer conditions and 2-propanol as the hydrogen source. The amino acid, through its chiral center and coordinating groups, helps stabilize the 16-electron active Ru complex needed for the hydrogen transfer step in the reduction process. On the other hand, incorrectly coordinated ligands (from mismatched configurations) may lead to inactive Ru complexes. The product's enantioselectivity was affected by the stereochemistry of the amino acid in the ligands, resulting in an efficient and stereoselective method for synthesizing chiral alcohols.

3.6. Miscellaneous reactions

In 1982, Kumada and colleagues presented novel amino acid-derived chiral phosphine ligands (**68**), featuring a distant chiral functional group for palladium-catalyzed asymmetric allylic alkylation.[70] The ligands used in this study were found to greatly enhance the reaction between allyl acetate and the enolate anion of 2-acetylcyclohexanone (**66**) [Scheme 10]. At the end of the reaction desired allylated product (**67**) was achieved with moderate enantiomeric excess. The highest *ee* (52%) was achieved at -50 °C using valine methyl ester and ephedrine ligands. The study highlighted the significance of ligand design in improving stereoselectivity through chelation.

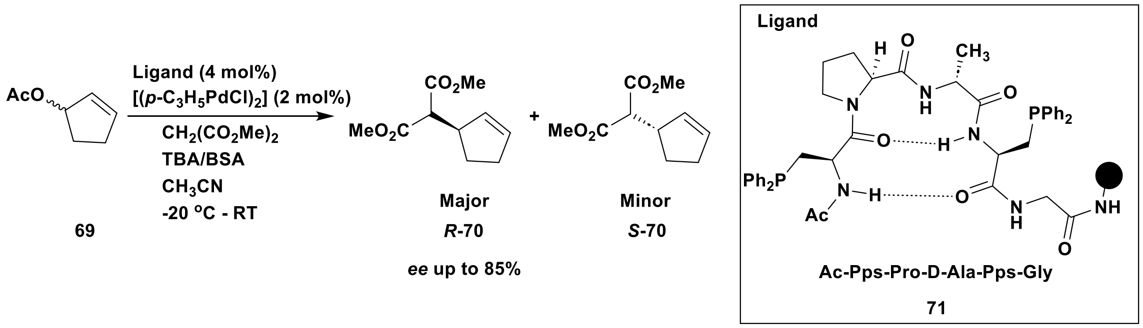


Scheme 10. Palladium–amino acid complex catalyzed asymmetric allylic alkylation.

Christoffers and co-workers have extensively developed chiral tridentate oxazoline ligands bearing thioether and heteroaryl donor groups.[71] Those are derived from amino acids like L-cysteine and L-methionine. Complexes of these ligands with transition metals such as Cu and Ni catalyze asymmetric Michael additions and related conjugate-addition reactions. These catalysts often yielded products with high stereocontrol. In this example, the amino acid residue provides both the chiral environment and part of the multidentate coordination site. That reinforced the idea of how amino acid-derived motifs can act as powerful ligands for asymmetric catalysis, in comparison to simple amino acid complexes.

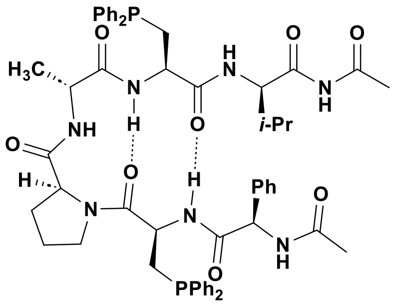
Edwards *et al.* introduced a rapid technique for producing poly-α-amino acids on solid supports by using lysine N-carboxyanhydride derivatives.[72] This method allows for the development of polymers with catalytic functions with palladium. The polymers undergo modification by incorporating phosphine groups to render them valuable as catalysts in palladium-catalyzed substitution processes. The authors demonstrated that these solid-supported phosphine ligands may be reused for more than one catalytic cycle with minimal loss of their catalytic activity.

A set of peptide sequences was developed by Gilbertson and co-workers to form a specific secondary structure (**71**) that can effectively bind with palladium [Figure 1. (c)].[20,73] This unique metal–ligand conformation facilitates the catalytic addition of dimethyl malonate to cyclopentenyl acetate (**69**), resulting in *R*-**70** up to 85% *ee* [Scheme 11]. They specifically investigated the changes in the β-turn secondary structure and substitutions in the amino acids that form the turn, especially around proline and D-amino acids. The ligand (D-Phg-Pps-Pro-D-Val-Pps-D-Leu-) was discovered to maintain its catalytic efficiency in both solid support as well as solution phase.



Scheme 11. Catalytic addition reaction of dimethyl malonate to cyclopentenyl acetate (**69**).

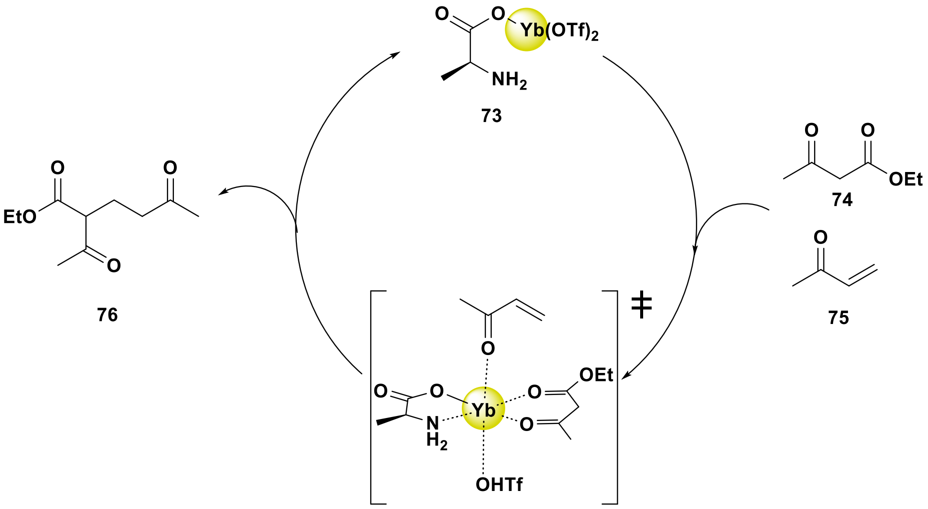
Continuation of the study, the same research group exemplified bisphosphine ligand systems for palladium-catalyzed additions to cyclic allyl acetates, achieving up to 95% *ee*.[74] Solid-phase peptide synthesis produced phosphine-containing amino acids for testing as different ligands. The optimum ligand was (Boc-D-Phg-Xps-Pro-D-Val-Pps-D-Leu-OMe) (**72**), shown to be highly selective in THF solvent and effective in polymer-supported and solution phase [Figure 13]. The study emphasized the significance of the β-turn secondary structure in generating high selectivity in catalytic processes.



72

Figure 13. (Boc-D-Phg-Xps-Pro-D-Val-Pps-D-Leu-OMe) ligand (**72**).

In addition, the Lewis acid-catalyzed Michael addition reactions were explored utilizing α-amino acid as a ligand (**73**). LindstrÖm and co-worker demonstrated ytterbium triflate ($Yb(OTf)_3$) as the source of the metal center, together with alanine as a ligand, showcasing a remarkable speed-up of the catalytic reaction between ethyl acetoacetate (**74**) and methyl vinyl ketone (**75**) [Scheme 12].[75] They observed that the second-order rate constant of the reaction increased by 138 times for alanine in a ytterbium triflate-catalyzed Michael addition, affording product **76**.

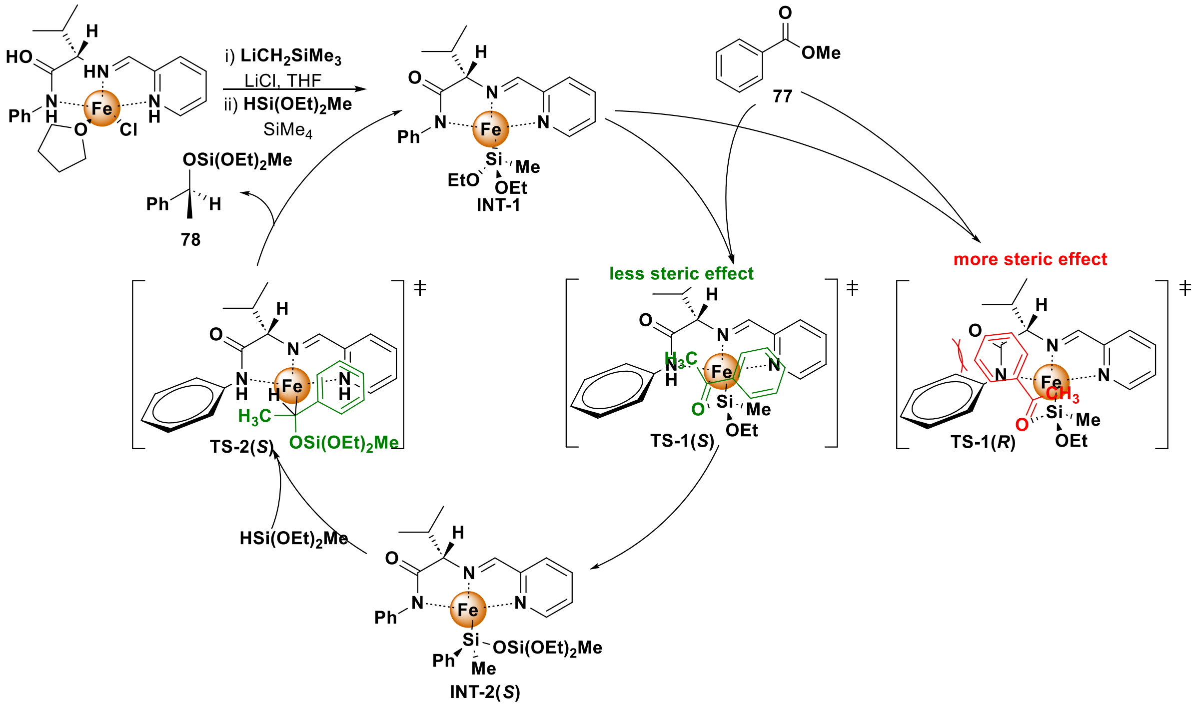


Scheme 12. Proposed mechanism for Michael addition reactions.

Amino acids like *N*-methylglycine, L-proline, and N, N-dimethylglycine act as bidentate ligands that chelate Cu, increasing its reactivity and stabilizing key intermediates during C–N bond formation.[76-79] These coordination complexes accelerate oxidative addition or facilitate nucleophilic attack, enabling milder Ullmann-type couplings. As a result, these amino acid-promoted systems deliver broad substrate scope and high efficiency under relatively gentle conditions.

In another example, L-proline acts as an effective bidentate ligand, greatly accelerating the Cu-catalyzed N-arylation of methyl 3-amino-1-benzothiophene-2-carboxylate.[80] L-proline effectively stabilized the active copper species and improved C–N bond formation. Under mild Ullmann-type conditions, this amino-acid-promoted system delivers broad substrate scope and moderate-to-high yields. This study showcases that amino acids enhance both reactivity and selectivity, outperforming classical diamine ligands. Overall, the methodology provides an alternative economical pathway to synthesize N-aryl benzothiophene derivatives.

A dual-functional MOF was demonstrated for the hydrosilylation and hydroboration of carbonyl compounds.[15] In the MOF, the amino acid served not only important component of the MOF skeleton but also played a key role in tuning the catalytic outcome through second coordination sphere interactions. This amino acid-derived MOF exhibited remarkable enantioselectivity, achieving over 99% *ee*, along with a high turnover number. Manna and co-workers also demonstrated that the MOF catalyst could be reused for at least 15 catalytic cycles without a decline in the enantioselectivity. In hydrosilylation of carbonyl (**77**), upon activation with $LiCH_2SiMe_3$, the MOF generates an Fe–CH_2SiMe_3 species, which reacts with $(OEt)_2MeSiH$ to form the active Fe–$Si(OEt)_2Me$ species (INT-1). The hydrosilylation then proceeds through carbonyl addition and σ-bond metathesis to yield hydrosilyl product **78**. In this pathway, INT-2(*S*) represents the resting state, and TS-1(*S*) establishes the enantioselectivity of the reaction [Scheme 13].

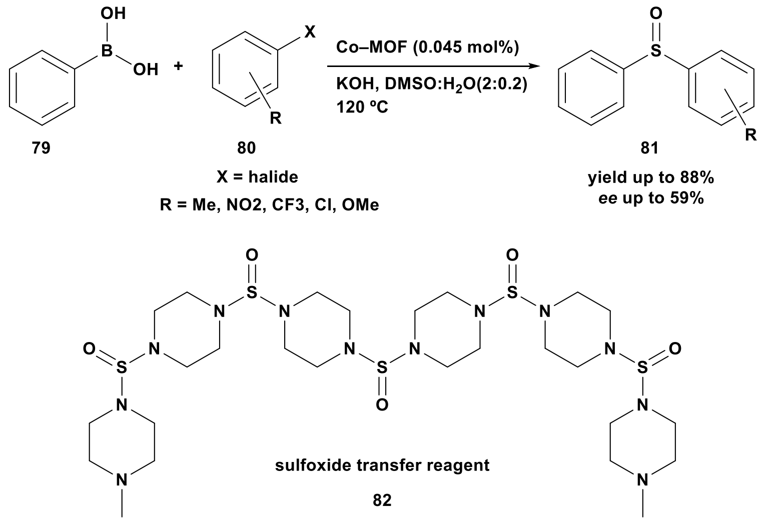


Scheme 13. Proposed catalytic cycle of hydrosilylation.

Bing-Feng *et al.* demonstrated monoprotected amino acids act as chiral bidentate ligands that coordinate to Pd.[81] These metal–amino acid complexes create a confined chiral environment required for selective C–H activation. Amino acids' amine and carboxylate groups bind cooperatively, steering the formation of a chiral palladacycle and controlling enantioselectivity. By restricting conformations and tuning steric bulk, these ligands enable efficient asymmetric activation of both C(sp^2)–H and C(sp^3)–H bonds.

In the same C–H activation field, the amino acid exemplified as a transient directing group, reversibly forming an imine that coordinates Pd, which enables selective C(sp^3)–H activation.[82] In benzylic arylation of aldehydes with 40–50 mol% glycine, products were obtained up to 83% isolated yield. For benzylic arylation of ketones, tuned conditions achieve 71% yield, demonstrating broad substrate compatibility. Amino acids such as L-tert-leucine further enable enantioselective C–H arylation with a 98:2 enantiomeric ratio.

Aspartic acid, as the chiral peptide linker, transfers asymmetry and provides coordination sites to the Co-decorated MOF [Figure 1. (e)].[23] The cubic MOF showed a high structural stability. It efficiently catalyzed asymmetric sulfoxidative cross-coupling, by reacting phenylboronic acid (**79**) with aryl halides (**80**) with very low catalytic loading using poly sulfinylpiperazine (**82**) as sulfoxide transfer reagent [Scheme 14]. The catalyst afforded product **81** in yields up to 88%, with moderate enantioselectivity and excellent recyclability without significant loss of activity.



Scheme 14. Co–MOF catalyzed asymmetric sulfoxidative cross-coupling reaction.

With time, more amino acid-functionalized MOFs emerged, which harness the reactivity of amino acids to create more selective and sustainable bioinspired catalysts. Based upon Zhu *et al.'s* findings,[42] L-serine-modified Zr-MOF creates natural pockets that accelerate multicomponent reactions, delivering up to 91% yield under simple conditions.[83] These examples of amino acid grafting show how gentle functionalities can improve reactivity inaccessible to the parent MOF. In the Cu–tryptophan MOF, the indole and carboxylate groups of the amino acid cooperate with Cu sites to activate CO_2 and epoxides.[84] This catalytic system achieved 95% conversion under mild, green conditions. This showcases that amino acids can transform metal sites into an efficient CO_2-utilizing catalyst.

Conclusions

Metal–amino acid complexes have emerged as powerful bioinspired catalysts. These advances include simple amino acid ligands, peptide scaffolds, supramolecular assemblies, and MOFs. These complexes cooperate with various interactions, like H-bonding, π–π stacking, cation-π effects, and PCET. These interactions create highly selective and efficient catalytic microenvironments. Their inherent chirality, second coordination spheres, and flexible metal coordination have enabled major catalytic advances.

Despite these achievements, there are several challenges remaining. The rational design of metal–amino acid complexes is complicated by obstacles such as multiple binding sites and competing coordination modes. Along with this, the understanding of the second coordination spheres for all examples is not clear yet. Moreover, while many systems demonstrate high selectivity in model reactions, translating this success to industrially relevant processes remains difficult. Future progress will require deeper mechanistic insight to address these gaps.

Looking ahead, the field stands at an exciting state. With the recent Nobel Prize spotlighting supramolecular chemistry, incorporating amino acid motifs into architectures such as cages and MOFs is expected to progress rapidly. These systems promise unprecedented control over substrate orientation and activation pathways. With deeper mechanistic insight and better structure–function understanding, this area will unlock new opportunities in sustainable and enzyme-inspired catalysis.

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References

1. Zhao, D. B.; Ding, K. L. *ACS Catal.* **2013**, *3*, 928-944.
   https://doi.org/10.1021/cs300830x
2. Sharma, S. K.; Paniraj, A. S. R.; Tambe, Y. B. *J. Agric. Food Chem.* **2021**, *69*, 14761-14780.
   https://doi.org/10.1021/acs.jafc.1c05553
3. Hou, C. C.; Wang, H. F.; Li, C. X.; Xu, Q. *Energy Environ. Sci.* **2020**, *13*, 1658-1693.
   https://doi.org/10.1039/c9ee04040d
4. Fang, Y. R.; Guo, Y. B. *Chin. J. Catal.* **2018**, *39*, 566-582.
   https://doi.org/10.1016/S1872-2067(17)62996-6
5. Shi, Z.; Yang, W.; Gu, Y.; Liao, T.; Sun, Z. *Adv. Sci.* **2020**, *7*, 2001069.
   https://doi.org/10.1002/advs.202001069
6. Kamanna, K. *Curr. Organocatal.* **2021**, *8*, 126-146.
   https://doi.org/10.2174/2213337207999201117093848
7. Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481-2495.
   https://doi.org/10.1016/S0040-4020(02)00122-9
8. Farkas, E.; Sóvágó, I. *Amino Acids, Pept., Proteins* **2015**, *39*, 21-67.
   https://doi.org/10.1039/978-1-84973-996-2-00021
9. Chin, J.; Lee, S. S.; Lee, K. J.; Park, S.; Kim, D. H. *Nature* **1999**, *401*, 254-7.
   https://doi.org/10.1038/45751
10. Song, Z.; Zhang, Q.; Wu, W.; Pu, Z.; Yu, H. *Front. Bioeng. Biotechnol.* **2023**, *11*, 1129149.
    https://doi.org/10.3389/fbioe.2023.1129149
11. Seerden, J.-P. G.; Scheeren, H. W. J. T. l. *Tetrahedron Lett.* **1993**, *34*, 2669-2672.

https://doi.org/10.1016/S0040-4039(00)77652-0

12. Paradowska, J.; Stodulski, M.; Mlynarski, J. *Adv. Synth. Catal.* **2007**, *349*, 1041-1046. https://doi.org/10.1002/adsc.200600581
13. Paganelli, S.; Marchetti, M.; Bianchin, M.; Bertucci, C. *J. Mol. Catal. A: Chem.* **2007**, *269*, 234-239. https://doi.org/10.1016/j.molcata.2007.01.027
14. Vicens, L.; Olivo, G.; Costas, M. J. A. C. I. E. *Angew. Chem., Int. Ed.* **2022**, *61*, e202114932. https://doi.org/10.1002/anie.202114932
15. Newar, R.; Akhtar, N.; Antil, N.; Kumar, A.; Shukla, S.; Begum, W.; Manna, K. *Angew. Chem., Int. Ed.* **2021**, *60*, 10964-10970. https://doi.org/10.1002/anie.202100643
16. Ghosh, T.; Ghosh, P.; Maayan, G. *ACS Catal.* **2018**, *8*, 10631-10640. https://doi.org/10.1021/acscatal.8b03661
17. Machan, C. W.; Yin, J.; Chabolla, S. A.; Gilson, M. K.; Kubiak, C. P. *J. Am. Chem. Soc.* **2016**, *138*, 8184-8193. https://doi.org/10.1021/jacs.6b03774
18. Sartor, D.; Saffrich, J.; Helmchen, G.; Richards, C. J.; Lambert, H. *Tetrahedron:Asymmetry* **1991**, *2*, 639-642. https://doi.org/10.1016/S0957-4166(00)86117-0
19. Itoh, S.; Kitamura, M.; Yamada, Y.; Aoki, S. *Chemistry* **2009**, *15*, 10570-84. https://doi.org/10.1002/chem.200900733
20. Agarkov, A.; Greenfield, S. J.; Ohishi, T.; Collibee, S. E.; Gilbertson, S. R. *J. Org. Chem.* **2004**, *69*, 8077-8085. https://doi.org/10.1021/jo049103g
21. Thoonen, S.; Tuck, K. L.; Turner, D. R. *Coord. Chem. Rev.* **2025**, *522*, 216203. https://doi.org/10.1016/j.ccr.2024.216203
22. Grajda, M.; Staros, G.; Jedrzejewska, H.; Szumna, A. *Inorg. Chem.* **2022**, *61*, 11410-11418. https://doi.org/10.1021/acs.inorgchem.2c01738
23. Ghorbani-Choghamarani, A.; Taherinia, Z. *Synth. Met.* **2020**, *263*, 116362-8. https://doi.org/10.1016/j.synthmet.2020.116362
24. Belokon, Y. N.; Chernoglazova, N. I.; Garbalinskaya, N. S.; Saporovskaya, M. B.; Kochetkov, K. A.; Belikov, V. M. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1986**, *35*, 2142-2144. https://doi.org/10.1007/BF00957546
25. Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98-122. https://doi.org/10.1002/jlac.19284600106
26. Avenier, F.; Ghattas, W.; Ricoux, R.; Mahy, J. P. *Vietnam J. Chem.* **2020**, *58*, 423-433. https://doi.org/10.1002/vjch.202000033
27. Corey, E.; Loh, T. P. J. J. o. t. A. C. S. *J. Am. Chem. Soc.* **1991**, *113*, 8966-8967. https://doi.org/10.1021/ja00023a066
28. Otto, S.; Boccaletti, G.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1998**, *120*, 4238-4239. https://doi.org/10.1021/ja972772+
29. Otto, S.; Engberts, J. B. J. J. o. t. A. C. S. *J. Am. Chem. Soc.* **1999**, *121*, 6798-6806. https://doi.org/10.1021/ja984273u
30. Ishihara, K.; Fushimi, M. J. O. L. *Org. Lett.* **2006**, *8*, 1921-1924. https://doi.org/10.1021/ol060651l
31. Ishihara, K.; Fushimi, M.; Akakura, M. *Acc. Chem. Res.* **2007**, *40*, 1049-1055. https://doi.org/10.1021/ar700083a

32. Furutani, M.; Sakamoto, S.; Kudo, K. *Heterocycles* **2009**, *78*, 1171-1176.
https://doi.org/10.3987/Com-08-11604
33. Yamashita, Y.; Yasukawa, T.; Yoo, W.-J.; Kitanosono, T.; Kobayashi, S. *Chem. Soc. Rev.* **2018**, *47*, 4388-448.
https://doi.org/10.1039/c7cs00824d
34. Nakagawa, M.; Nakao, H.; Watanabe, K.-i. *Chem. Lett.* **1985**, *14*, 391-394.
https://doi.org/10.1246/cl.1985.391
35. Fernandez-Lopez, R.; Kofoed, J.; Machuqueiro, M.; Darbre, T. *Eur. J. Org. Chem.* **2005**, *2005*, 5268-5276.
https://doi.org/10.1002/ejoc.200500352
36. Darbre, T.; Machuqueiro, M. *Chem. Commun.* **2003**, 1090-1091.
https://doi.org/10.1039/B301117H
37. Kofoed, J.; Darbre, T.; Reymond, J. L. *Chem. Commun.* **2006**, 1482-1484.
https://doi.org/10.1039/b600703a
38. Penhoat, M.; Barbry, D.; Rolando, C. *Tetrahedron Lett.* **2011**, *52*, 159-162.
https://doi.org/10.1016/j.tetlet.2010.11.014
39. Xu, Z.; Daka, P.; Wang, H. *Chem. Commun.* **2009**, 6825-6827.
https://doi.org/10.1039/b912728c
40. Daka, P.; Xu, Z.; Alexa, A.; Wang, H. *Chem. Commun.* **2011**, *47*, 224-226.
https://doi.org/10.1039/c0cc00917b
41. Stodulski, M.; Jaźwiński, J.; Mlynarski, J. *Eur. J. Org. Chem.* **2008**, 5553-5562.
https://doi.org/10.1002/ejoc.200800726
42. Zhu, J.; Meng, X.; Liu, W.; Qi, Y.; Jin, S.; Huo, S. *RSC Adv.* **2022**, *12*, 21574-21581.
https://doi.org/10.1039/d2ra03747e
43. Zheng, K.; Liu, X.; Feng, X. *Chem. Rev.* **2018**, *118*, 7586-7656.
https://doi.org/10.1021/acs.chemrev.7b00692
44. Baskakov, D.; Herrmann, W. A. *J. Mol. Catal. A Chem.* **2008**, *283*, 166-170.
https://doi.org/10.1016/j.molcata.2007.12.006
45. Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755-756.
https://doi.org/10.1021/ja003698p
46. Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362-13363.
https://doi.org/10.1021/ja021081x
47. Kacprzynski, M. A.; Kazane, S. A.; May, T. L.; Hoveyda, A. H. *Org. Lett.* **2007**, *9*, 3187-90.
https://doi.org/10.1021/ol071331k
48. Breit, B.; Laungani, A. C. *Tetrahedron:Asymmetry* **2003**, *14*, 3823–3826.
https://doi.org/10.1016/j.tetasy.2003.10.002
49. Laungani, A. C.; Breit, B. *Chem. Commun.* **2008**, 844-846.
https://doi.org/10.1039/b716529c
50. Laungani, A. C.; Slattery, J. M.; Krossing, I.; Breit, B. *Chemistry* **2008**, *14*, 4488-502.
https://doi.org/10.1002/chem.200800359
51. Arya, P.; Rao, N. V.; Singkhonrat, J.; Alper, H.; Bourque, S. C.; Manzer, L. E. *J. Org. Chem.* **2000**, *65*, 1881-1885.
https://doi.org/10.1021/jo991621h
52. Maux, P. L.; Srour, H. F.; Simonneaux, G. *Tetrahedron* **2012**, *68*, 5824-5828.
https://doi.org/10.1016/j.tet.2012.05.014
53. Valodkar, V. B.; Tembe, G. L.; Ravindranathan, M.; Rama, H. S. *React. Funct. Polym.* **2003**, *56*, 1-15.

https://doi.org/10.1016/S1381-5148(03)00048-8

54. Cussó, O.; Ribas, X.; Lloret-Fillol, J.; Costas, M. J. A. C. I. E. *Angew. Chem., Int. Ed.* **2015**, *54*, 2729-2733. https://doi.org/10.1002/anie.201410557
55. Cussó, O.; Giuliano, M. W.; Ribas, X.; Miller, S. J.; Costas, M. J. *Chem. Sci.* **2017**, *8*, 3660-3667. https://doi.org/10.1039/C7SC00099E
56. Evangelisti, F.; Moré, R.; Hodel, F.; Luber, S.; Patzke, G. R. *J. Am. Chem. Soc.* **2015**, *137*, 11076-11084. https://doi.org/10.1021/jacs.5b05831
57. Boer, D.; Stegman, H.; Peeters, C. J. C.; Siegler, M. A.; Hetterscheid, D. G. H. *Eur. J. Inorg. Chem.* **2024**, *27*, e202300475. https://doi.org/10.1002/ejic.202300475
58. Ruan, G. L.; Ghosh, P.; Fridman, N.; Maayan, G. *J. Am. Chem. Soc.* **2021**, *143*, 10614-10623. https://doi.org/10.1021/jacs.1c03225
59. Ruan, G. L.; Engelberg, L.; Ghosh, P.; Maayan, G. *Chem. Commun.* **2021**, *57*, 939-942. https://doi.org/10.1039/d0cc06912d
60. Pahar, S.; Maayan, G. *Chem. Sci.* **2024**, *15*, 12928-12938. https://doi.org/10.1039/d4sc01182a
61. Prathap, K. J.; Maayan, G. *Chem. Commun.* **2015**, *51*, 11096-11099. https://doi.org/10.1039/c5cc04266f
62. Mohan, D. C.; Sadhukha, A.; Maayan, G. *J. Catal.* **2017**, *355*, 139-144. https://doi.org/10.1016/j.jcat.2017.09.018
63. Stamatin, Y.; Maayan, G. *Eur. J. Org. Chem.* **2020**, *2020*, 3147-3152. https://doi.org/10.1002/ejoc.201901739
64. Xu, S.; Wu, H.; Liu, S.; Du, P.; Wang, H.; Yang, H.; Xu, W.; Chen, S.; Song, L.; Li, J.; Shi, X.; Wang, Z. G. *Nat. Commun.* **2023**, *14*, 4040. https://doi.org/10.1038/s41467-023-39779-6
65. Sharma, A.; Gore, P. M.; Kandasubramanian, B. *J. Environ. Chem. Eng.* **2021**, *9*, 104798. https://doi.org/10.1016/j.jece.2020.104798
66. Facchetti, S.; Jurcik, V.; Baldino, S.; Giboulot, S.; Nedden, H. G. n.; Zanotti-Gerosa, A.; Blackaby, A.; Bryan, R.; Boogaard, A.; McLaren, D. B.; Moya, E.; Reynolds, S.; Sandham, K. S.; Martinuzzi, P.; Baratta, W. *Organometallics* **2016**, *35*, 277-287. https://doi.org/10.1021/acs.organomet.5b00978
67. Bogevig, A.; Pastor, I. M.; Adolfsson, H. *Chemistry* **2004**, *10*, 294-302. https://doi.org/10.1002/chem.200305553
68. Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem. - Eur. J.* **2003**, *9*, 4031-4045. https://doi.org/10.1002/chem.200304900
69. Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem. Commun.* **2002**, 2046-2047. https://doi.org/10.1039/B206471E
70. Hayashi, T.; Kanehira, K.; Tsuchiya, H.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1162-1164. https://doi.org/10.1039/c39820001162
71. Christoffers, J.; Mann, A.; Pickardt, J. *Tetrahedron* **1999**, *55*, 5377-5388. https://doi.org/10.1016/S0040-4020(99)00235-5
72. Edwards, C. W.; Shipton, M. R.; Wills, M. *Tetrahedron Lett.* **2000**, *41*, 8615-8619. https://doi.org/10.1016/s0040-4039(00)01512-4
73. Gilbertson, S. R.; Collibee, S. E.; Agarkov, A. *J. Am. Chem. Soc.* **2000**, *122*, 6522-6523.

https://doi.org/10.1021/ja992306f

74. Greenfield, S. J.; Agarkov, A.; Gilbertson, S. R. *Org. Lett.* **2003**, *5*, 3069-3072. https://doi.org/10.1021/ol035097j
75. Aplander, K.; Ding, R.; Lindstrom, U. M.; Wennerberg, J.; Schultz, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4543-4546. https://doi.org/10.1002/anie.200700560
76. Zhang, H.; Cai, Q.; Ma, D. *Chem. Inform.* **2005**, *36*, 5164-5173. https://doi.org/10.1002/chin.200545082
77. Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Chem. Inform.* **2005**, *36*, 496-499. https://doi.org/10.1002/chin.200528048
78. Zhu, W.; Ma, D. *Chem. Commun.* **2004**, 888-889. https://doi.org/10.1039/b400878b
79. Ma, D.; Cai, Q. *Chem. Inform.* **2004**, *35*, 128-130. https://doi.org/10.1002/chin.200421098
80. Kederienė, V.; Jaglinskaitė, I.; Voznikaitė, P.; Rousseau, J.; Rollin, P.; Šačkus, A.; Tatibouët, A. *Molecules* **2021**, *26*, 6822. https://doi.org/10.3390/molecules26226822
81. Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882-4886. https://doi.org/10.1002/anie.200801030
82. Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. *Science* **2016**, *351*, 252-256. https://doi.org/10.1126/science.aad7893
83. Ghobakhloo, F.; Mohammadi, M.; Ghaemi, M.; Azarifar, D. *ACS Appl. Nano Mater.* **2024**, *7*, 1265-1277. https://doi.org/10.1021/acsanm.3c05230
84. Jeong, G. S.; Kathalikkattil, A. C.; Babu, R.; Chung, Y. G.; Won Park, D. *Chin. J. Catal.* **2018**, *39*, 63-70. https://doi.org/10.1016/S1872-2067(17)62916-4

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