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Review

Natural Chiral Ligand Strategy: Metal-Catalyzed Reactions with Ligands Prepared from Amino Acids and Peptides

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Abstract: Amino acids and peptides are readily available biomolecules and can function as chiral ligands for transition metal catalysis. An example is the copper complex catalyzed 1,4-addition of dialkylzinc to acyclic enones, which employs peptide ligands. This review provides a dataset of amino acids and peptides reported in the literature proving to be effective ligands for metal-centered catalysts. Several parameters were highlighted, including amino acid combination, metal atoms, carboxyl and amino protecting groups, modification of natural amino acids, and the mechanism of catalysis. Along with analyzing physical-chemical properties, the SMILES representation for each amino acid and/or peptide was generated and made available online, providing an easy-to-use means of training machine learning models. This review offers an opportunity for the development of more efficient peptide ligands for enantioselective metal-centered catalysts. The available online dataset is a reliable manually curated table, it enables the benchmark for comparison of new terminal functional groups. Moreover, the review provides insight into the structures of the more successful peptide ligands and can be used as the foundation for the development of the next generation of peptide-based chiral ligands.

Keywords: enantioselective; peptide ligands; metal complexes; catalysts; catalyzed reactions

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Citation: Gung, B.W.; Kubesch, C.; Bernstein, G. Natural Chiral Ligand Strategy: Metal-Catalyzed Reactions with Ligands Prepared from Amino Acids and Peptides. *Catalysts* **2024**, *14*, 813. https://doi.org/10.3390/catal14110813

Academic Editors: Gyula Pályi and Tomasz K. Olszewski

Received: 30 August 2024
Revised: 25 October 2024
Accepted: 6 November 2024
Published: 12 November 2024

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1. Introduction

During our search for chiral ligands for gold catalysts [1], we surveyed the related literature on both natural and man-made amino acids and peptide ligands that were examined by previous investigators as chiral ligands [2–26]. Although the use of amino acids and peptides as metal ligands with chiral centers is an excellent idea, there is a lack of systematic compilation and analysis of the scattered literature reports. This inspired us to prepare a review in this area for future development in this field. Amino acids and peptides are capable of forming catalytic complexes with a metal atom. Many examples of amino acids and peptide ligands have been experimentally validated by the Hoveyda group [2–14]. Various features of those metal atom–peptide ligand complexes examined in this review include variations in metal atoms, N-terminus functions, sidechain functions, C-terminus functions, modifications of amino acids, and catalyzed reactions. The reported peptide ligands in this review are capable of forming catalytic metal complexes for various enantioselective organic reactions. In addition, cross-coupling reactions such as Sonogashira and Suzuki reactions were also carried out successfully using amino acid and peptide ligands [17]. Mono-N-protected amino acids (MPAAs) as bidentate ligands for Pd-catalyzed C−H functionalization were first introduced by the Yu laboratory [20,21], and subsequently established as a successful ligand group by this and several other groups [22–26]. MPAA ligands have the potential to enable the discovery of many new and useful metal-catalyzed C−H functionalization reactions, which have been well reviewed [21]. As a whole, amino acid and peptide ligands reported so far offer insight into existing design successes, which are important for the development of new enantioselective chiral ligands. The review is

based on the reported success of enantioselective transformations promoted by the metal complexes with the chiral ligands prepared from amino acids and peptides. The N- and C-terminus group functions reported in these studies provide an opportunity for analysis of terminus function–catalytic activity relationships.

2. Scope of Review

This review includes the following metal complexes: copper (112, number of examples in the data table), zirconium (55), titanium (28), ruthenium (12), hafnium (4), aluminum (1), and palladium (46). The experimental examples included in this review were organized as a data table and have been submitted to the repository: Mendeley Data (DOI:10.17632/ywg8bck2zv.1). The data table features 12 columns with the following headings for the description of each metal–ligand complex: (column 1) three-letter amino acid and peptide code; (column 2) one-letter amino acid and peptide code; (column 3) SMILES (simplified molecular-input line-entry system) formula; (column 4) metal atoms; (column 5) N-terminal functions; (column 6) sidechain protecting groups; (column 7) C-terminal functions; (column 8) sidechain modifications; (column 9) catalyzed reaction types; (column 10) reaction chemical yields; and (column 11) reaction enantioselectivity, as well as (column 12) the literature references. Some of the reported chemical yields and enantioselectivity differences are due to substrate structure variations if there are no ligand changes indicated.

In this review, we condense the dataset into a manageable-sized table (see Table 1) and present the key elements in these catalytic complexes including the amino acids and peptide sequences, the metal atoms, the N-terminal functions, and the type of reactions catalyzed by the peptide–metal atom complexes. In Sections 3.1–3.6, each representative metal complex with the example of the highest enantioselectivity where applicable is shown. For cross-coupling reactions, where enantioselectivity was not applicable, the reactions with the highest chemical yields are depicted. In the figures, the structural features of these ligands for each metal type are shown with the reaction type and chemical yields, as well as enantioselectivity where available, in addition to the peptide sequences.

Table 1. Condensed Data of Peptide Ligands and Metal Atoms Capable of Forming Enantioselective Catalysts.

Peptide [Reference]	Metal	N-Terminus Function	Reaction Type
(S)-Val-(S)-Glu-Gly [2]	Al	imine	Addition of TMSCN to ketone
(S)-Val-(S)-Phe-Gly [5]	Cu	Pyridinyl-imine	allylic substitution
(S)-Val-(S)-Phe-Gly [5]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of RZnR to cyclic enones
(S)-Val-(S)-Phe-Gly [5]	Cu	2-(Diphenyl)phosphino-phenyl-imine	Addition of RZnR to ketones
(S)-Val [5]	Cu	Pyridinyl-imine	Allylic substitution
(S)-Val [5]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of RZnR to cyclic enones
(S)-Val [5]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of RZnR to acyclic enones
(S)-Val [4]	Ti	2-hydroxy-5-methyoxy-phenyl-imine	Strecker cyanohydrin formation
(S)-Val [10]	Zr	2-hydroxyphenyl-imine	Imine alkylation
(S)-Val [16]	Ru	N-Boc	Reduction of acetophenone
(S)-Val [16]	Ru	N-Boc	Reduction of acetophenone
(R)-Val [16]	Ru	N-Boc	Reduction of acetophenone
(R)-Val [16]	Ru	N-Boc	Reduction of acetophenone
(S)-Thr-(R)-Val [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of RZnR to heterocycle
(S)-Thr-(R)-Val [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of RZnR to cyclic enones
(S)-Ala-(S)-Val [6]	Cu	2-hydroxynaphthalene-1-imine	Allylic alkylations
(S)-Val-(S)-Ala [6]	Cu	2-(Hydroxy)phenyl-imine	ACA of RZnR to cyclic enones
(S)-Val-(S)-Ala [6]	Cu	2-(Amino)phenyl-imine	ACA of RZnR to cyclic enones
(S)-Val-(S)-Ala [6]	Cu	2-(Methylamino)phenyl-imine	ACA of RZnR to cyclic enones
(S)-Leu-(S)-Ala [6]	Cu	2-(Methylamino)phenyl-imine	ACA of RZnR to cyclic enones
(S)-Leu-(S)-Trp [6]	Cu	2-(Methylamino)phenyl-imine	ACA of RZnR to cyclic enones
(S)-Val-(S)-Thr [4]	Ti	2-hydroxy-3,5-dichloro-phenyl-imine	Strecker cyanohydrin formation

Table 1. *Cont.*

Peptide [Reference]	Metal	N-Terminus Function	Reaction Type
(S)-Val-(R)-Thr [4]	Ti	2-hydroxy-5-methyoxy-phenyl-imine	Strecker cyanohydrin formation
(S)-Val-(S)-Thr [4]	Ti	2-hydroxy-3-fluoro-phenyl-imine	CN addition to epoxides
(S)-Val-(S)-Thr [4]	Ti	2-hydroxy-3-fluorophenyl-imine	Addition of TMSCM to epoxides
(S)-Val-Gly [4]	Ti	2-hydroxy-5-methyoxy-phenyl-imine	Strecker cyanohydrin formation
(S)-Val-Gly [10]	Zr	2-hydroxyphenyl-imine	Imine alkylation
(S)-Phe-(S)-Phe [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of (R)2Zn to cyclic enones
(S)-Ala-(S)-Phe [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of (R)2Zn to cyclic enones
(S)-Thr-(R)-Thr [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of (R)2Zn to cyclic enones
(S)-Asp-(S)-Phe [13]	Cu	2-hydroxy-5-methylphenyl-imine	Allylic alkylations
(S)-Asp-(S)-Phe [13]	Cu	2-hydroxy-5-tertbutylphenyl-imine	Allylic alkylations
(S)-Thr-(S)-Trp [13]	Cu	2-hydroxynaphthalene-imine	Allylic alkylations of olefins
(S)-Val-(S)-Thr-Gly [13]	Cu	2-hydroxyphenyl-imine	Addition of CN to arylimines
(S)-Val-(S)-Thr-Gly [14]	Ti	2-hydroxyphenyl-imine	Addition of CN to arylimines
(S)-Val-(S)-Thr-Gly [14]	Ti	2-hydroxy-5-methoxyphenyl-imine	Addition of CN to alkenylimines
(S)-Val-(S)-Thr-Gly [14]	Ti	2-hydroxy-3,5-dichlorophenyl-imine	Cyanide addition to imines
(S)-Val-(S)-Phe [5]	Cu	Pyridinyl-imine	Allylic substitution
(S)-Val-(S)-Phe [5]	Cu	Isopropoxy-Pyridinyl-imine	Allylic substitution of alkenes
(S)-Val-(S)-Phe [5]	Cu	Isopropoxy-Pyridinyl-imine	Allylic substitution of alkenes
(S)-Val-(S)-Phe [5]	Cu	Isopropoxy-Pyridinyl-imine	Allylic substitution of alkenes
(S)-Val-(S)-Phe [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of RZnR to cyclic enone
(S)-Val-(S)-Phe [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of RZnR to nitroalkenes
(S)-Val-(S)-Phe [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of RZnR to acyclic enamine
(S)-Val-(S)-Phe [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of RZnR to acyclic enone
(S)-Val-(S)-Phe [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of RZnR to cyclic enones
(S)-Val-(S)-Phe [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	Addition of RZnR to ketones
(S)-Val-(S)-Phe [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	Addition of RZnR to ketones
(S)-Val-(S)-Phe [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of RZnR to cyclic enones
(S)-Val-(S)-Phe [9]	Cu	2-(Diphenyl)phosphino-phenyl-imine	ACA of RZnR to cyclic enones
(S)-Val-(S)-Phe [10]	Hf	2-hydroxy-5-methoxy-amine	Imine alkylation
(S)-Val-(S)-Phe [11]	Ti	2-hydroxy-3,5-ditertbutylphenyl-imine	Addition of TMSCM to epoxides
(S)-Val-(S)-Phe [11]	Ti	2-hydroxynaphthalenephenyl-imine	Addition of TMSCM to epoxides
(S)-Val-(S)-Phe [10]	Zr	2-hydroxy-5-methoxyphenyl-amine	Alkylation of ketoimine esters
(S)-Val-(S)-Phe [10]	Zr	2-hydroxyphenyl-imine	Imine alkylation
(S)-Val-(S)-Phe [10]	Zr	2-hydroxy-3,5-ditertbutylphenyl-amine	Imine alkylation
(S)-Val-(S)-Phe [10]	Zr	2-hydroxyphenyl-amine	Imine alkylation
(S)-Val-(S)-Phe [10]	Zr	2-hydroxy-5-methoxyphenyl-amine	Alkylation of ketoimine esters
(S)-Val-(S)-Phe [13]	Cu	2-hydroxyphenyl-imine	Allylic alkylations of olefins
(S)-Val-(S)-Phe [12]	Zr	2-hydroxy-5-methoxyphenyl-amine	Alkylation of ketoimines
(S)-Val-(S)-Phe [12]	Zr	2-hydroxy-3,5-dichlorophenyl-amine	Alkylation of ketoimines
(S)-Val-(S)-Phe [12]	Zr	2-hydroxy-3,5-dibromophenyl-amine	Alkylation of ketoimines
(S)-Val-(S)-Phe [12]	Zr	2-hydroxy-3-nitro-5-bromophenyl-amine	Alkylation of ketoimines
(S)-Val-(S)-Phe [12]	Zr	2-hydroxy-5-nitrophenyl-amine	Alkylation of ketoimines
(S)-Val-(S)-Phe [12]	Zr	2-hydroxy-3,5-ditertbutylphenyl-amine	Alkylation of ketoimines
(S)-Val-(S)-Phe [12]	Zr	2-hydroxynaphthalenephenyl-amine	Alkylation of ketoimines
(S)-Val-(S)-Phe [12]	Zr	2-hydroxy-3,5-ditertbutylphenyl-amine	Alkylation of ketoimines
(S)-Val-(S)-Phe [12]	Zr	2-hydroxy-5-methoxyphenyl-amine	Alkylation of ketoimine esters
(S)-Val-(S)-Phe [12]	Zr	2-hydroxy-3,5-ditertbutylphenyl-amine	Alkylation of ketoimine esters
(S)-Val-(S)-Phe [12]	Zr	2-hydroxy-3,5-ditertbutylphenyl-amine	Synthesis of N-heterocycles
(S)-Ala [16]	Ru	N-Boc	Reduction of acetophenone
(S)-Leu [16]	Ru	N-Boc	Reduction of acetophenone
(S)-Ile [16]	Ru	N-Boc	Reduction of acetophenone
(S)-Phe [16]	Ru	N-Boc	Reduction of acetophenone
Phe-Val [17]	Pd	NHC-pyridine	Sonogashira cross-coupling
Phe-Val [17]	Pd	NHC-pyridine	Suzuki cross-coupling
Phe-Val [17]	Pd	NHC-pyridine	Suzuki cross-coupling
Asp-(D)-Pro [15]	Cu	TETRAMETHYLGUANIDINE	C-O bond formation
Asp-(D)-Pro-Aib [15]	Cu	TETRAMETHYLGUANIDINE	C-O bond formation
Asp-(D)-Pro-Aib [15]	Cu	TETRAMETHYLGUANIDINE	C-O bond formation

Table 1. *Cont.*

Peptide [Reference]	Metal	N-Terminus Function	Reaction Type
Asp-(D)-Pro-Cle [15]	Cu	TETRAMETHYLGUANIDINE	C-O bond formation
Asp-(D)-Pro-(D)-Ala [15]	Cu	TETRAMETHYLGUANIDINE	C-O bond formation
Asp-(D)-Pro-Gly [15]	Cu	TETRAMETHYLGUANIDINE	C-O bond formation
Asp-(D)-Pro-Acpc [15]	Cu	TETRAMETHYLGUANIDINE	C-O bond formation
Asp-(D)-Pro-Ala [15]	Cu	TETRAMETHYLGUANIDINE	C-O bond formation
Asp-(D)-Pro-Aib-(D)-Ala-Ala [15]	Cu	TETRAMETHYLGUANIDINE	C-O bond formation
Asp-(D)-Pro-Aib-(D)-Ala [15]	Cu	TETRAMETHYLGUANIDINE	C-O bond formation
Asp-(D)-Pro-Aib-Ala [15]	Cu	TETRAMETHYLGUANIDINE	C-O bond formation
Asp-(D)-Pro-Aib-(D)-Leu [15]	Cu	TETRAMETHYLGUANIDINE	C-O bond formation
Asp-(D)-Pro-Aib-(D)-Phe [15]	Cu	TETRAMETHYLGUANIDINE	C-O bond formation

Abbreviations: 1. Aib, α-aminoisobutyric acid; 2. Cle, cycloleucine (1-aminocyclopentane-1-carboxylic acid); 3. Acpc, 1-amino-cyclopropane-1-carboxylic acid.

This review mainly covers chiral ligands prepared from natural amino acids and peptides. For ligands prepared from synthetic peptides, please see an excellent earlier review [27].

3. Applications of Amino Acid and Peptide Ligands in Metal Catalysis

Several research groups investigated the employment of amino acids and peptides as metal ligands to prepare catalysts for organic reactions forming the basis for this review [2–17]. We will discuss the synthesis of different metal complexes and their uses in nucleophilic additions including CN^- and dialkylzinc reagents addition to imines, conjugate additions, enantioselective reductions, and cross-coupling reactions.

While the amino and carboxyl groups of amino acids and peptides may not be suitable for forming complexes with metal atoms, the transformation of the amino group into an imine or an enamine function enhances the catalytic complex formation. In some cases, the conversion of the -NH_2 group into a secondary amine function with a bulky substituent improved the enantioselectivity of the resulting complexes. The C-terminus carboxyl group is commonly protected as a bulky amide. In certain examples, the carboxyl group was attached to a polymer so that the catalysts could be easily recycled.

A more focused description of each metal complex is described in the following subsections. By comparisons of reaction examples in each metal group, the reactions with higher chemical yield in combination with a higher enantioselectivity where applicable are depicted in the figures.

3.1. Ti-Catalyzed Cyanide Addition to Imines

Snapper, Hoveyda, and coworkers pioneered the application of amino acids and peptides as metal ligands [2–14]. They reported studies of Ti-catalyzed addition of cyanide to imines in the presence of titanium complexes with Schiff base peptide ligands, Figure 1 [2–4]. An important practical observation of the Ti-catalyzed process was that dropwise addition of an alcohol to the reaction mixture was required to achieve significant levels of conversion. Molecular modeling studies involving imine and peptide Schiff base suggested that the association of substrate to one face of the distorted octahedral Ti–Schiff base complex was energetically more favorable. More importantly, if metal substrate association occurred from the alternative face of the Ti–peptide complex, the carbonyl of the amino acid at position two could not promote C-C bond formation readily, because the bulky amino acid substituent would be projected toward the catalyst structure during cyanide delivery. The imine substrate, in its lower energy trans configuration, coordinates in a manner that minimizes steric interactions with the chiral Ti–peptide complex. It was in such a substrate–metal complex that the amide carbonyl of the amino acid could readily reach and deliver HCN to the C=N bond to produce the major product enantiomer.

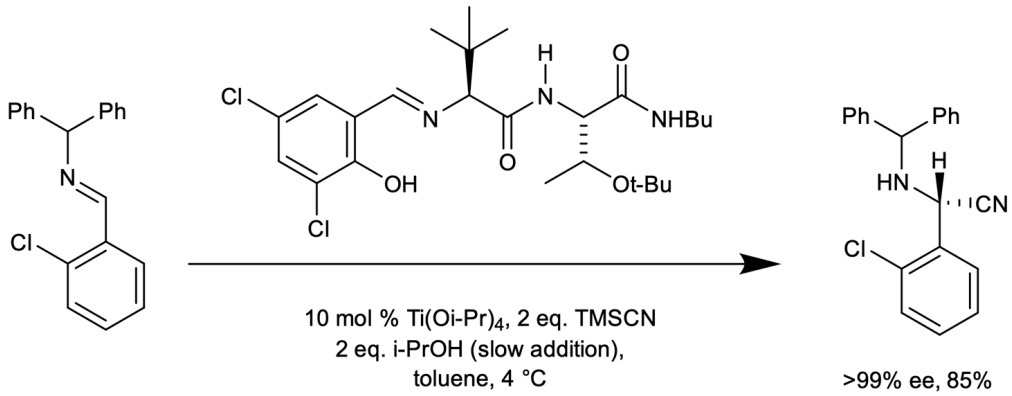

Figure 1. Ti-catalyzed cyanide addition to imines was achieved in high reactivity and enantioselectivity in the presence of the dipeptide. Peptide Schiff base serves as bifunctional catalysts in asymmetric Strecker reaction. This ligand includes a sidechain modification: t-Bu for i-Pr in valine [2–4].

3.2. Cu-Catalyzed Asymmetric Conjugate Addition of Alkylzinc to Disubstituted Cyclic Enones

Hoveyda and coworkers studied the catalytic enantioselective conjugate addition of dialkylzinc reagents to cyclic enones [7]. These transformations were promoted by $(CuOTf)_2$-C_6H_6 in conjunction with peptide-based chiral phosphine ligands (Figure 2). Their initial experiments with the phenol Schiff base did not yield good enantioselectivity. The authors considered that the phenol Schiff base might be suitable for association with early transition metals, the corresponding P-containing chiral ligand such as what is shown in Figure 2 should provide a "softer" site of binding and might be more appropriate for late transition metals. Accordingly, the dipeptide P-containing ligand was prepared from commercially available 2-(diphenylphosphino)-benzaldehyde. Screening of conditions established the optimum Cu salt and solvent. Chiral phosphine dipeptide and CuOTf promoted enantioselective conjugate additions to cyclic enones. As illustrated in Figure 2, cyclopentenone underwent Cu-catalyzed conjugate additions in the presence of 1.0 mol % $(CuOTf)_2$-C_6H_6 and 2.4 mol % dipeptide catalyst (72% conv and >98% ee).

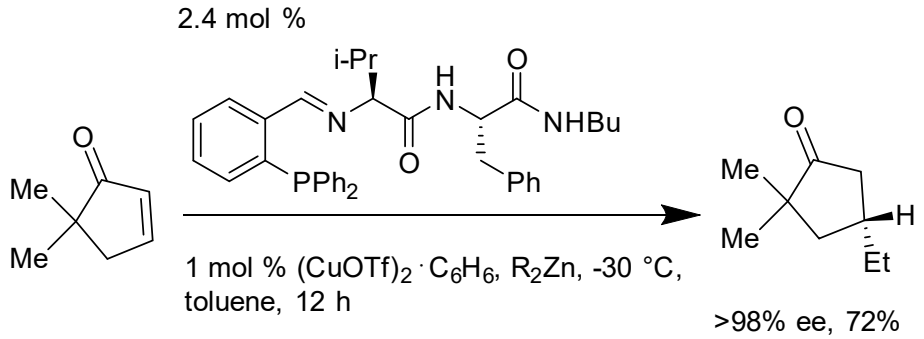

Figure 2. Cu-catalyzed asymmetric conjugate addition of alkylzinc to disubstituted cyclic enones. Valine-phenylalanine dipeptide phosphine in the presence of $(CuOTf)_2 \cdot C_6H_6$ promotes 1,4-addition of alkylzinc to cyclic enones in high enantioselectivity. The corresponding salicyl and pyridyl ligands produced racemic products for this reaction [7].

3.3. Zr- and Hf-Catalyzed Enantioselective Additions of R_2Zn to Imines

Snapper, Hoveyda, and coworkers also reported Zr-catalyzed and Hf-catalyzed enantioselective additions of R_2Zn to imines, Figures 3 and 4 [10]. A significant difference in the efficiency of the formation of amines bearing an ester group, compared to that of amides indicates that subtle structural variations within substrate molecules (e.g., ester vs. amide terminus) could have a notable influence on the efficiency of catalytic asymmetric processes.

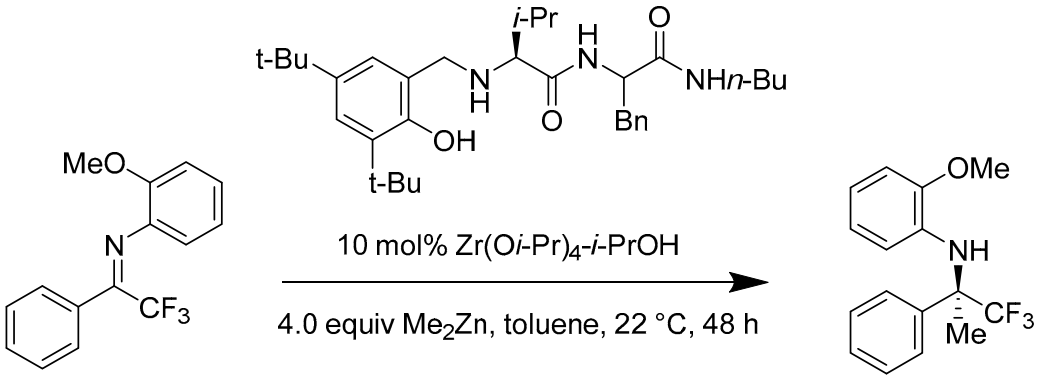

Figure 3. Zr-catalyzed enantioselective additions of Et_2Zn to imines were achieved in the presence of the dipeptide. It can be readily applied to aromatic imines with high chemical yield and enantioselectivity [12].

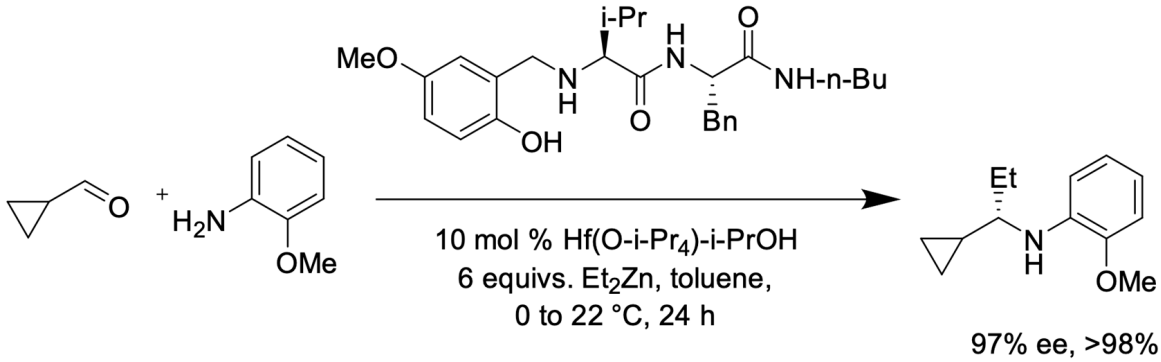

Figure 4. Hf-catalyzed enantioselective additions of Et_2Zn to imines were achieved in high chemical yield and enantioselectivity in the presence of the dipeptide. It can be applied to aliphatic imines with the same high chemical yield and enantioselectivity as with aromatic imines [10].

It was observed that the Zr-catalyzed imine alkylation (Figure 3) could be readily applied to aliphatic, as well as aromatic substrates. However, reactions involving aliphatic imines often lead to the isolation of the desired optically enriched amines in moderate yields. Their experimental results indicated that the Hf-catalyzed method (Figure 4) afforded optically enriched aliphatic amines in significantly higher yields with similar levels of asymmetric induction as observed with the original Zr-catalyzed protocol.

In summary, the investigators carried out enantioselective alkylations of aryl-, alkyl-, and alkynylimines efficiently in the presence of amino acid-based chiral ligands. Such transformations could be promoted in the presence of $Zr(O\text{-}i\text{-}Pr)_4$; however, significantly improved yields were observed when $Hf(O\text{-}i\text{-}Pr)_4$ was used. The structural features of the dipeptide Schiff base ligands include the presence of a chiral amino acid-2 moiety that bears a sufficiently bulky substituent. The absolute stereochemical identity of the amino acid-2 moiety is critical in determining the identity of the major product enantiomer. Mechanistic working models that account for the above structural requirements as well as observed enantioselectivities were provided.

3.4. Ru-Catalyzed Enantioselective Reduction of Acetophenone

Adolfsson and co-workers studied the enantioselective Ru-catalyzed reduction of ketones, Figure 5 [16]. In this study, the investigators presented the preparation and evaluation of a novel class of pseudo-symmetric peptide-like ligands that, when combined with $[\{RuCl_2(p\text{-cymene})\}_2]$, resulted in catalysts exhibiting superior activity and selectivity in ketone reductions.

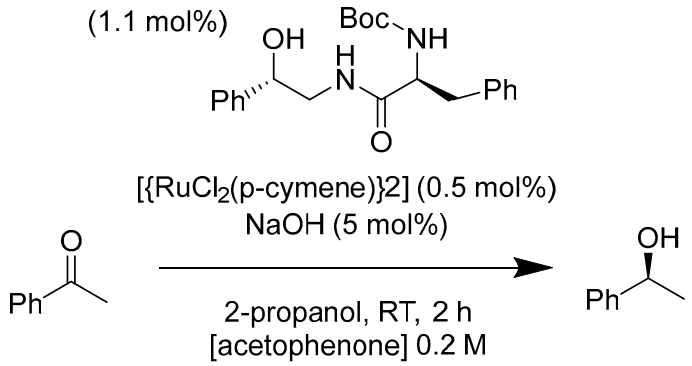

Figure 5. Ru-catalyzed enantioselective reduction of acetophenone was achieved in high chemical yield and enantioselectivity in the presence of the complex. Ligands based on N-Boc-protected phenylalanine and 2-amino-1-phenylethanol gave superior catalysts concerning conversion and selectivity [16].

A library of 36 pseudo-dipeptides was prepared by the investigators, and these ligands were evaluated using the reduction of acetophenone as the model reaction. Catalysts generated from L-amino acids and (S)-amino alcohols generally gave the product alcohol with very good enantioselectivity (>90%), whereas using the mismatched ligand combination led to considerably lower enantioselectivity of 1-phenylethanol.

The authors proposed an explanation for their results. The "dipeptides" were proposed to be potential tridentate ligands and, therefore, several structurally different metal complexes could be formed. Assuming that a 16-electron ruthenium complex was present before the formation of the active ruthenium hydride. This 16-electron complex could be formed if only two out of the three available donors of the dipeptide ligand were coordinated to the metal center. Hence, if the initially formed, catalytically active ruthenium complex rearranges into other complexes over time, these new species could have different catalytic properties. The observed activity of the catalyst was rather sensitive towards the structure of the ligand. In cases in which the "wrong" diastereomer of the ligand was employed, low conversion and low enantioselectivity were obtained. These mismatched ligands favored the formation of such inactive complexes. The matched ligands on the other hand, could significantly decrease the rate of such processes from favorable steric interactions. The activity and selectivity obtained using either the matched or the mismatched ligand could also be explained by the inherent pseudo-symmetry of the ligands (Figure 5). In the matched cases, the combination of L-amino acids with (S)-amino alcohols, the ligands possessed pseudo-C2-symmetry, which could reduce the number of possible catalytically active complexes. In the mismatched cases, the pseudo-meso configuration of the ligands would open up for the formation of a significantly higher number of complexes.

3.5. Pd-Catalyzed Sonogashira and Suzuki Cross Coupling Reactions

Melda and Worm-Leonhard studied the Sonogashira and Pd-catalyzed Suzuki cross-coupling reactions, Figures 6 and 7 [17]. In this study, the investigators sought a synthetic method that provided access to unsymmetrical, N-substituted, imidazolium ions containing a terminal-protected carboxylic acid functional group. Such imidazolium ions would serve as N-heterocyclic carbene (NHC) precursors. By using commercially available methyl or tert-butyl esters of different amino acids, amino-acid-derived imidazoles were synthesized in a one-pot reaction. In order to allow for the formation of bis(imidazolium) salts, commercially available 2,6-bis(bromomethyl)pyridine was employed. To investigate the potential of the new imidazolium ion building blocks as N-heterocyclic carbene ligands in the solid phase, two peptides were synthesized. The dipeptide (Phe-Val) was chosen as a tether between the NHC and the solid support, thereby providing an attachment point.

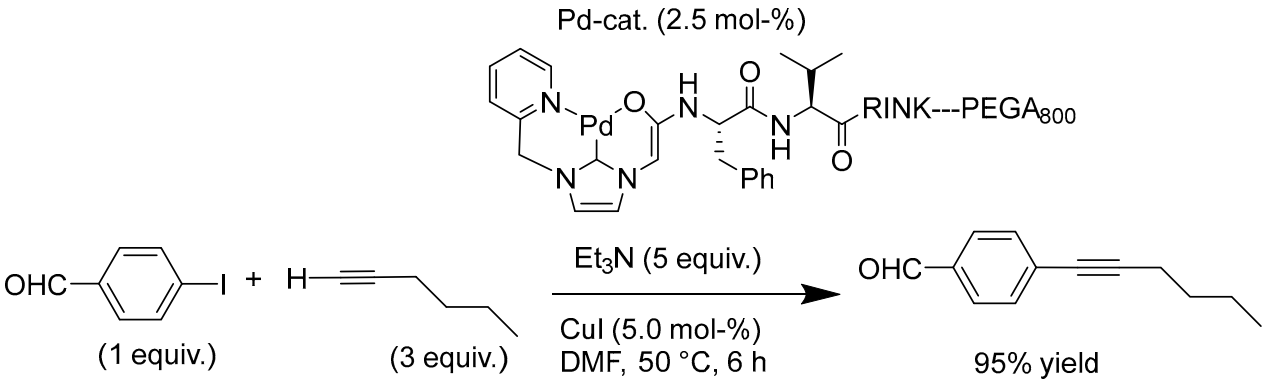

Figure 6. Pd-catalyzed Sonogashira cross-coupling reaction. Ligands are based on NHC-pyridine at the N-terminus and the peptide is attached to Rink-amide linker to amino-functionalized PEGA resin. The polymer attached catalysts can be recycled. The catalysts also gave high chemical yields [17].

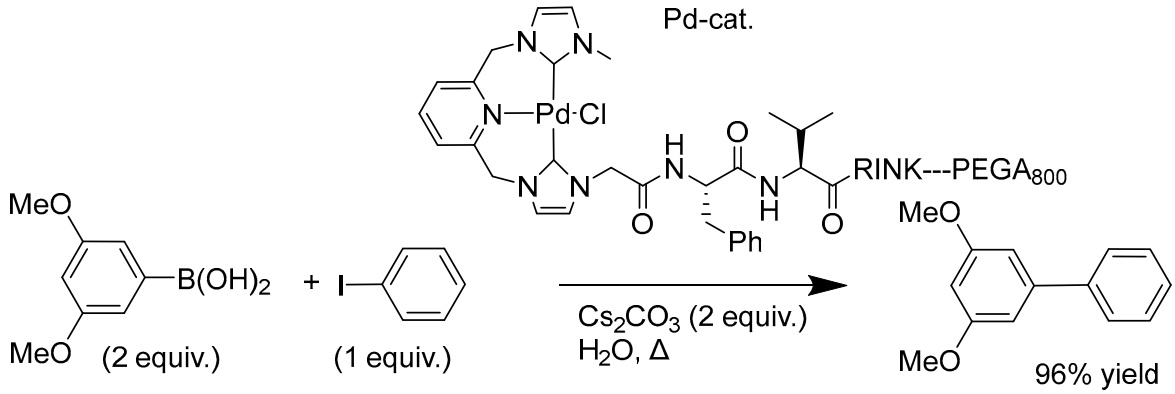

Figure 7. Pd-catalyzed Suzuki cross-coupling reaction. Ligands are based on bis-(NHC)-pyridine at the N-terminus and the peptide is attached to the Rink-amide linker by amino-functionalized PEGA resin. The polymer-attached catalysts can be recycled. High chemical yields were reported [17].

The investigators synthesized a series of functionalized imidazolium-ion building blocks, containing a pyridine moiety and carboxylic acid functional group. These compounds could serve as NHC precursors. They were attached to a dipeptide, which was attached to a polymer. Subsequent carbene formation was achieved by treatment with a strong base, 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), followed by complexation to palladium (II) on solid support. These new and efficient palladium NHC catalysts were successfully applied to Sonogashira and Suzuki cross-coupling reactions. The catalysts proved to be stable toward TFA treatment when released from the solid support and stable in aqueous media, thus allowing for the Suzuki cross-coupling reactions to be performed in water. No loss of catalytic activity was observed when the catalyst was recycled and subjected to repetitive cycles of cross-coupling reactions in water.

The investigators did not report any studies on synthesizing axially chiral biphenyl compounds using their catalysts. It would be interesting to employ starting materials with ortho-substituted aromatic boronic acids and iodobenzenes to see if any enantiomerically enriched biphenyl products can be produced. This would be a reasonable extension because the catalysts (Figure 7) contain chiral elements.

3.6. Cu-Catalyzed Enantioselective Cross-Coupling C−O Bond Formation

Miller and co-workers studied a series of enantioselective C−O bond cross-coupling reactions [15]. The development in this methodology was multifunctional peptide-based ligands that allowed highly selective, intermolecular Cu-catalyzed cross-coupling of phenolic nucleophiles. Symmetry-breaking reactions of diaryl methines such as the starting material shown in Figure 8 give chiral diaryl ethers as the major product with significant

levels of enantioselectivity (Figure 8). These reactions represented the pioneering reports of metal-catalyzed, enantioselective C−O bond cross-coupling that involved peptides as chiral ligands.

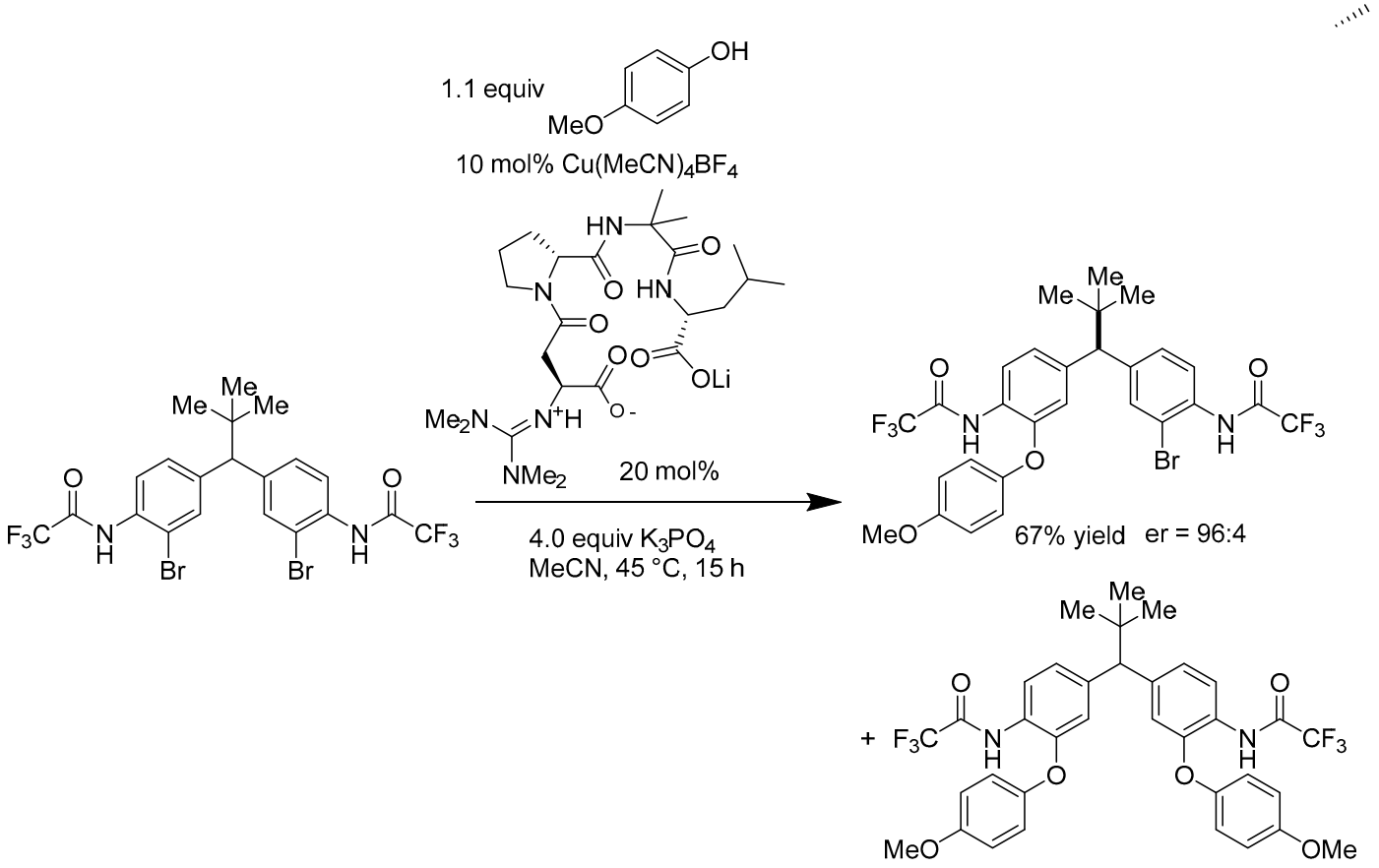

Figure 8. Cu-catalyzed de-symmetrization through remote cross-coupling for intermolecular enantioselective C−O bond formation. Ligands based on N-terminus guanidinylated tetrapeptide are shown to have higher levels of enantioselectivity [15].

In their study, a guanidinylated peptide ligand/Cu-based system was reported for the process of enantioselective C−O bond forming cross-coupling reactions. One of the features of the system was a symmetry-breaking reaction of remote sites within diaryl methine derivatives. The selectivity was related to enantiotopic group differentiation, influenced by the length and stereochemistry of the peptide ligand. The scope of phenolic nucleophiles was also reported to reveal a tolerance of a series of electronically varied substituents, as well as variable steric hindrance. Multifunctional substrates were also demonstrated to participate in the reaction. The functionalization of phenols in the presence of other nucleophilic functional groups was suggested to be predictable using the working model. The scope of the process concerning the symmetrical diaryl methines was examined as well. Aryl chloride substitution was found to be inert in the presence of aryl bromides, and steric demands of t-Bu were well-tolerated at the methine moiety.

3.7. Mono-Nitrogen-Protected Amino Acids (MPAAs) as Bidentate Ligands for Pd-Catalyzed C−H Functionalization

In addition, studies by the Yu group and others [20–25] investigated the effects of palladium and mono-N-protected amino acids (MPAA) ligands on the functionalization and alkylation of sp^3 and sp^2 C-H bonds, Figure 9. In their study, the investigators were interested in improving Pd-catalyzed C-H functionalization reactions for better enantioselectivity and site selectivity by using MPAA ligands. These specific ligands are known for their ability to participate in catalytic steps in C-H activation. In terms of alkylating

sp^3 and sp^2 C-H bonds, a specific acridine ligand was used to form a weakly coordinating amide directing group.

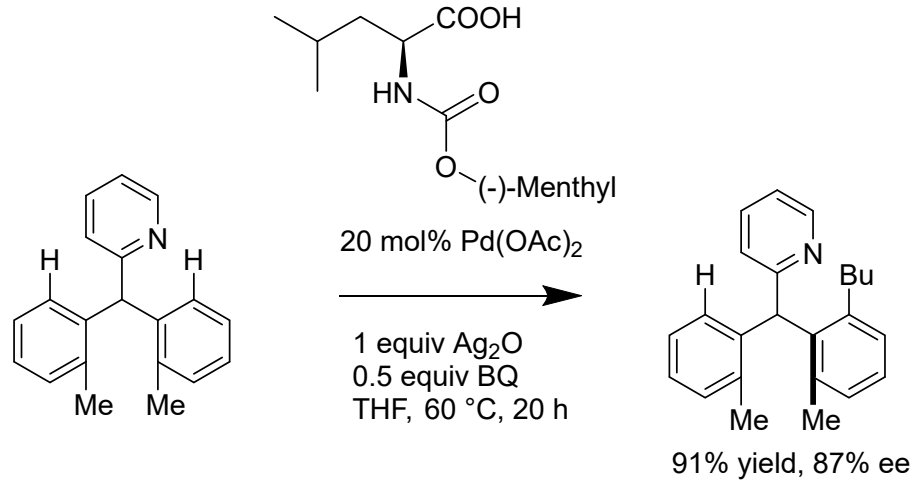

Figure 9. Mono-N-protected amino acids (MPAAs) as bidentate ligands for Pd-catalyzed C−H functionalization [20,21].

3.8. Vanadium-Based Catalysts for Asymmetric Epoxidation

Chiral amino acid-based hydroxamic acids (Figure 10) were found to be effective asymmetric catalysts for the epoxidation of allylic alcohols by the Yamamoto group [28]. The mild reaction conditions, low temperature (0 °C), low requirement of loading quantity (1 mol % of vanadium), and halogen-free solvent (toluene), broaden the utility of this approach.

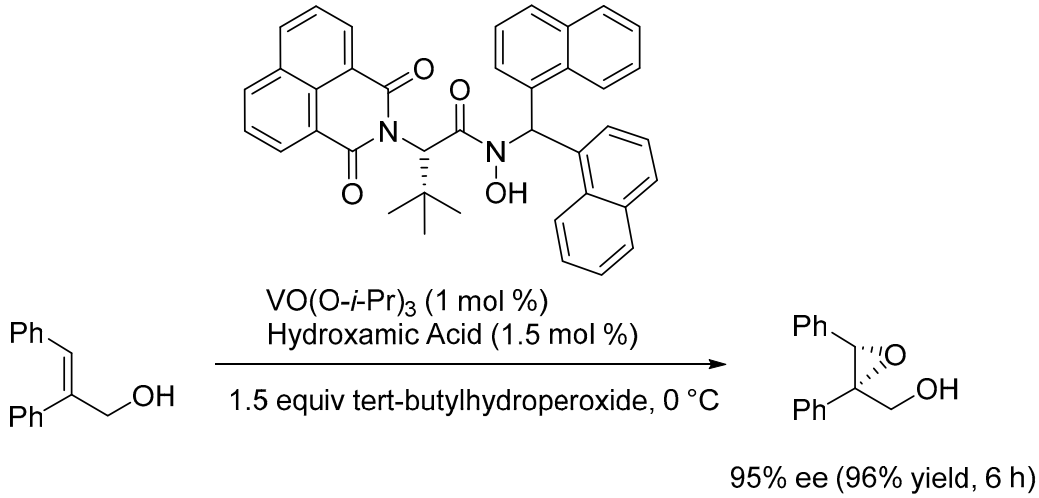

Figure 10. Vanadium-based catalysts for asymmetric epoxidation. Chiral alpha-amino acid-based hydroxamic acid ligands are efficient catalysts for the asymmetric epoxidation of allylic alcohols.

4. Conclusions

In conclusion, this review of metal catalysis utilizing chiral ligands prepared from natural and synthetically modified peptides and amino acids provides a systematic collection of studies in this field from previously scattered literature. These versatile chiral ligands prepared from peptides and amino acids provide catalytic metal complexes that catalyze a wide range of reactions. Most of the metal complexes prepared in this fashion have demonstrated remarkable efficacy in producing reaction products with high yields and enantioselectivity. Many reactions discussed in this review have the potential to be widely applicable to organic synthetic methods. Some examples of C-C bond formation are

the copper-catalyzed asymmetric conjugate additions of alkylzinc to disubstituted cyclic enones and Pd-catalyzed Sonogashira and Suzuki cross-coupling reactions.

Additionally, in the data Table available online, the incorporation of SMILES formulas allows for the development of machine learning in further studies. Artificial intelligence provides a tool to investigators in this field for better predicting reaction products as well as reaction outcomes in terms of yield and enantioselectivities [18,19]. In the field of organic synthesis, AI has great potential for synthetic chemists to prepare different products in more efficient ways.

These reactions show great potential to address challenges in various synthetic targets and can create new opportunities for future technology and application development. The usage of chiral ligands prepared from peptides and amino acids in metal catalysis is positioned well to have a significant impact on the development of synthetic chemistry moving forward.

Author Contributions: C.K.: Data curation, structure drawing, writing—original draft. G.B.: data curation, structure drawing. B.W.G.: conceptualization, investigation, supervision, funding acquisition, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Dean's Scholar Fund of Miami University, Oxford, OH, USA.

Data Availability Statement: No new data were created or analyzed in this study.

Conflicts of Interest: The authors declare no conflict of interest.

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