

Metallopeptides for Enantioselective Catalysis

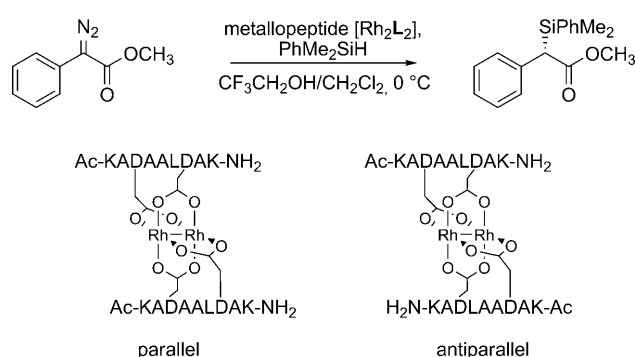
Gerard Roelfes^{*[a]}

Metalloenzymes are the benchmark catalysts for efficient enantioselective chemical transformations and, as such, are a source of inspiration for catalyst design. As in transition metal asymmetric catalysis, the first coordination sphere, that is, the ligands provided by the protein that bind to the metal center and tune its electronic properties, determine the catalytic activity of metalloenzymes. However, the key to their high efficiency and selectivity is the second coordination sphere; a combination of additional interactions, such as hydrogen bonding, electrostatic, hydrophobic, and steric interactions, with the metal-bound substrate and/or activated complex.^[1] The increasing appreciation of the importance of second coordination sphere interactions in catalysis has given rise to a new approach to catalysis, which aims to create hybrid catalysts that merge the catalytic power of transition metal complexes with the high activities and enantioselectivities of metalloenzymes. To date, considerable effort has been devoted to the design of artificial metalloenzymes; these are existing proteins to which a transition metal complex is anchored in a covalent or supramolecular fashion.^[1,2] This research has given rise to a number of highly enantioselective hybrid catalysts.^[3] One of the promises in this field yet to be fulfilled is that these artificial metalloenzymes can be optimized further by using the power of directed evolution methodologies.^[4] However, the technical challenges involved are formidable and, despite some progress,^[5] have still to be overcome.

An alternative approach to hybrid catalysts involves metallopeptides. The advantage of peptides is that they are readily available and libraries can be prepared using the power of parallel automated peptide synthesis. Whereas organocatalytic peptides are abundant and have been demonstrated to give high *ee* values and catalytic activities,^[6] the field of metallopeptides for asymmetric catalysis has so far remained rather unexplored. The reported examples all include nonproteinogenic metal-coordinating moieties, such as phosphines^[7] and pyridines,^[8] as these generally provide superior metal coordination, especially to late transition metals such as rhodium. Ball and co-workers realized that the carboxylate-containing side chains of proteinogenic amino acids such as aspartate (Asp) and glutamate (Glu) can be used to introduce a dirhodium tetracarboxylate complex into a helical peptide scaffold.^[9] Dirhodium tetracarboxylates are excellent catalysts for a wide variety of enantioselective reactions, particularly those involving carbenoid intermediates, such as cyclopropanations and X–H

insertion reactions.^[10] Sambasivan and Ball have now reported the successful application of these dirhodium-containing peptides in catalytic enantioselective Si–H insertion reactions.^[11]

Their first design involved a nonapeptide **L1**, with the sequence KADAALDAK. The carboxylate moieties provided by the aspartate side chains in the *i* and *i*+4 position, were used as the bridging ligands to bind [Rh₂(OAc)₂] in a 1:1 peptide–dirhodium complex [Rh₂(OAc)₂(**L1**)]. When applied to a benchmark Si–H insertion reaction (Scheme 1), a modest but promis-



Scheme 1. Benchmark catalytic enantioselective Si–H insertion reaction and the two isomeric parallel and antiparallel metallopeptide catalysts [Rh₂(**L1**)₂] (**A** and **B** isomers, arbitrary order). **L1** is a nonapeptide with the sequence KADAALDAK. The structures of the **A** and **B** isomers are not yet known.

ing 32% *ee* was obtained for the reaction product. In a key design step, the remaining acetate ligands were exchanged by carboxylates from the peptide by forming a 2:1 peptide–dirhodium complex [Rh₂(**L1**)₂], resulting in the formation of two isomeric metallopeptides, in which the two peptide strands had a parallel or antiparallel orientation with respect to each other. The two isomers, designated **A** and **B**, were separated, but it has not been established which one is the parallel or the antiparallel isomer. Both isomers were tested in catalysis and gave rise to different enantioselectivities in the Si–H insertion reaction. Interestingly, the *ee* obtained with isomer **B** was significantly higher than that obtained with [Rh₂(OAc)₂(**L1**)].

Encouraged by these results, a small library of metallopeptides was prepared. Based on a previously computed structure,^[12] positions *i*–1 and *i*+3 were selected as positions for introducing mutations, since their side chains are in proximity of the metal centers. The screening of both the **A** and **B** isomers of 22 metallopeptide variants identified several catalysts that gave a high *ee* values in the benchmark reaction; up to 92% *ee* was obtained when using the **B** isomer of the metallopeptide of **L21** (Figure 1). Comparison of the sequence of the metallopeptides giving the highest enantioselectivities re-

[a] Dr. G. Roelfes

Stratingh Institute for Chemistry, University of Groningen
Nijenborgh 4, 9747 AG Groningen (The Netherlands)
Fax: (+31) 50-363-4296
E-mail: J.G.Roelfes@rug.nl

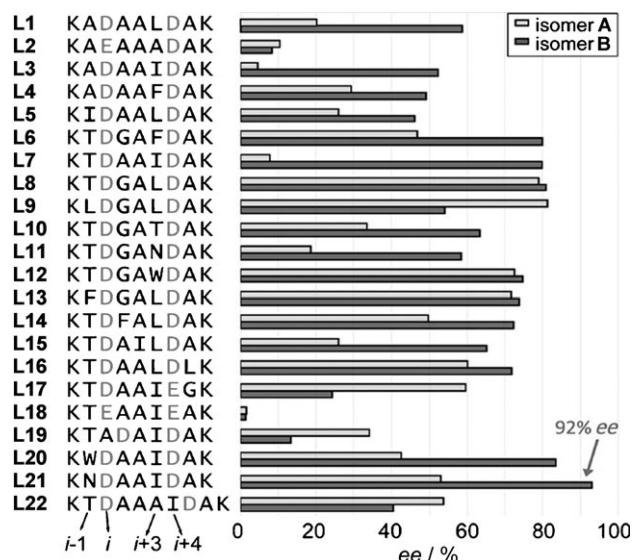


Figure 1. Optimization of the nonapeptide ligands **L**. Reprinted with permission from reference [10]. Copyright 2010, American Chemical Society.

vealed some intriguing trends. Sterically demanding hydrophobic amino acids at position *i*+3 were found to give rise to the best results. Particularly interesting, however, was the observation that threonine, asparagine, and tryptophan were the preferred residues at position *i*−1. This finding suggests that, in addition to steric interactions, other second coordination sphere interactions with the bound substrate or activated complex, such as hydrogen bonding, may also be important in achieving high enantioselectivity. Other findings indicated that the nature and spacing of the metal-coordinating residues were of particular importance. Inferior catalysts resulted from replacing the metal-coordinating Asp residues with Glu, or from increasing the distance between the metal-coordinating carboxylate moieties.

The substrate scope of the catalytic asymmetric Si–H insertion reaction was investigated using isomer **B** of $[\text{Rh}_2(\text{L21})_2]$, which gave the highest ee values in the benchmark reaction. Excellent ee values were obtained by using a variety of aryl- and vinyl-substituted diazoacetates; in the latter case, an ee of 97% was obtained. One example of an alkyl-substituted diazoacetate was reported, which gave rise to lower enantioselectivity.

Sambasivan and Ball have convincingly demonstrated the potential of metallopeptides for enantioselective catalysis. An

open question remains the structure of the metallopeptide isomers **A** and **B**, in particular whether the peptides are oriented parallel or antiparallel, which will significantly change the catalyst structure. Even though isomer **B** gave the highest ee in the majority of cases, this was by no means a general trend. By using the power of parallel automated peptide synthesis, it is expected that this elegant and versatile strategy will give access to new enantioselective catalytic reactions, including transformations for which there is currently no alternative using conventional asymmetric catalysis, thereby taking full advantage of the readily tunable second coordination sphere.

Keywords: enantioselectivity • enzyme catalysis • insertion • peptides • rhodium

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