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Metallopeptides for Asymmetric Dirhodium Catalysis

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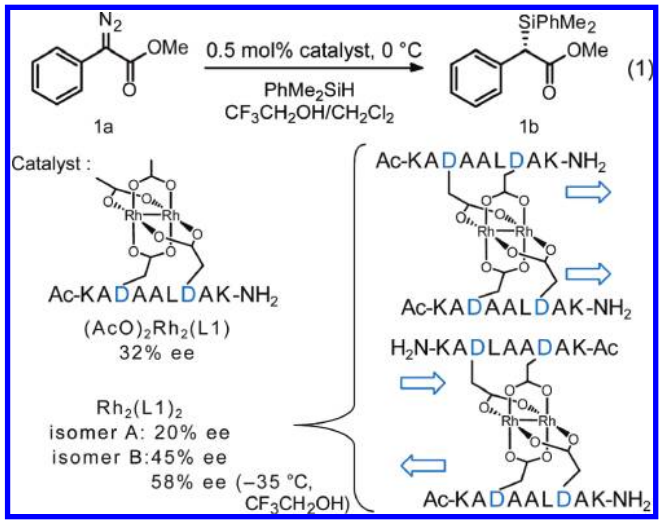
Abstract: Natural peptide sequences ligate to dirhodium centers through two bridging aspartate side chains, creating a macromolecular ligand framework with helical structure. The generation of a small peptide library allowed optimization of peptide sequence and produced an efficient catalyst for enantioselective carbenoid insertion into Si−H bonds. Analysis of the library indicates that the *i*−1 and *i*+3 positions of nonapeptides have the most significant effect on enantioselectivity, though the structural basis for selectivity is different at each of the positions.

Polypeptides are the predominant biological solution to chemo- and stereoselective ligand design. They are modular structures allowing facile side-chain variation and have been developed as useful asymmetric catalysts.[1] Chiral ligand design remains a largely empirical exercise, so straightforward access to large ligand libraries is often critical to successful reaction development. Despite the obvious attraction of peptide ligands, extending the example of natural metalloenzymes to synthetic capabilities has been limited.[2] In this paper, we describe the use of carboxylate-containing peptides as ligands for asymmetric dirhodium catalysis. The few examples of stereoselective organometallic catalysis with peptide ligands have typically employed non-natural amino acids containing phosphine[3] or pyridine[4] groups or attachment of whole coordination complexes to proteins by covalent[5] or supramolecular[6] means.

Dirhodium tetracarboxylates are important catalysts for asymmetric synthesis,[7] catalyzing useful reactions of diazo compounds that are compatible with diverse functional groups. We have recently demonstrated that the side-chain carboxylates of a peptide can be used as bidentate ligands for dirhodium,[8] affording metallopeptides that retain catalytic activity in diazo decomposition reactions.[8c] We chose the insertion of $PhMe_2SiH$ into methyl α-diazophenylacetate[9] as a model reaction to explore the selectivity of dirhodium metallopeptide catalysts.

Our ligand design began with the notion that peptides with defined secondary structure would be good candidates for asymmetric induction. We examined nonapeptide ligands such as KA**D**AAL**D**AK (**L1**) that feature carboxylate-containing residues (glutamate, E or aspartate, D) with *i*, *i*+4 spacing to induce α-helical structure.[8b] The complex $Rh_2(OAc)_2$(**L1**), with a chelating bis-carboxylate peptide ligand,[10] was accessed[8a] by treatment of the peptide ligand with $Rh_2(OAc)_2(tfa)_2$ and provided a modest 32% ee (eq 1). In an attempt to improve chiral recognition, we turned to the *bis*-peptide complex Rh_2(**L1**)$_2$, accessible by reaction of the peptide with $Rh_2(tfa)_4$. The *bis*-peptide complexes are formed as mixtures of parallel and antiparallel isomers (eq 1), which are separable by HPLC.[11] The two isomers of Rh_2(**L1**)$_2$ provided different levels of enantioinduction (20% vs 45%), and the ee afforded by Rh_2(**L1**)$_2$-isoB could be improved to 58% by dropping the reaction temperature to −35 °C and changing the solvent to pure CF_3CH_2OH.[12] The improved enantioselectivity afforded by



Rh_2(**L1**)$_2$-isoB relative to the *mono*-peptide complex led us to pursue a broader screen of *bis*-peptide complexes (Figure 1).

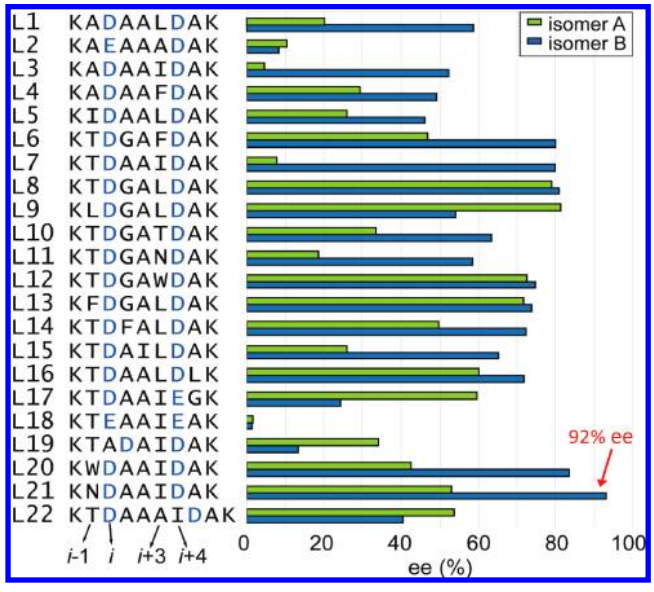


Figure 1. Optimization of a peptide ligand for eq 1. Reaction conditions: 0.5 mol % $Rh_2(L)_2$ catalyst at −35 °C in CF_3CH_2OH. All ligands are C-terminal $-NH_2$ amides and N-terminal acetyls. Lysine side chains are capped as Cbz carbamates to improve solubility.

Circular dichroism studies indicated that even very short peptides with *i*, *i*+4 carboxylate spacing become strongly helical upon metal binding (see the Supporting Information).[8a] Based on computed structures of the helical metallopeptides,[8b] we identified the residues in positions *i*−1 and *i*+3 as positioning side chains in proximity to the metal center and thus as likely to impact stereoselectivity

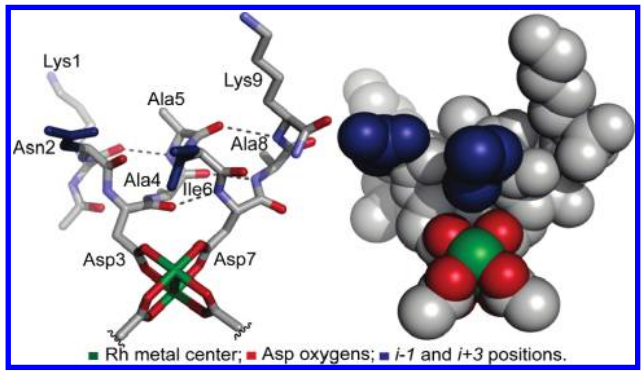
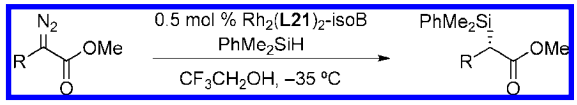


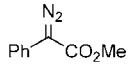
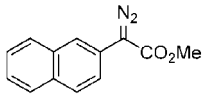
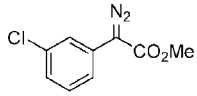
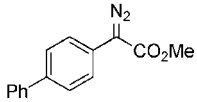
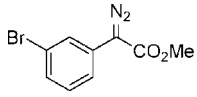
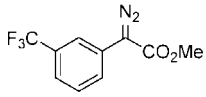
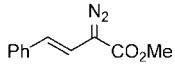
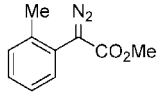
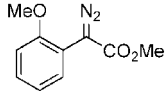
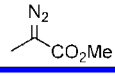
Figure 2. Tube and space-filling models for **L21** bound to a dirhodium center. The key $i-1$ and $i+3$ residues are shown in blue. For clarity, Cbz groups, hydrogen atoms, and the second peptide chain are not shown.

(Figure 2). We synthesized a small peptide library and found that the predicted $i-1$ and $i+3$ positions have the most significant effect on enantioselectivity, even when compared to the other residues adjacent to aspartate ligation sites, $i+1$ and $i+5$ (Figure 1, **L14**, **L16**).

Although the enantioselectivity of the complex Rh_2(**L1**)$_2$ was modest, our peptide screen soon arrived at a new peptide, **L21**, that provides the silane product in 92% ee (Figure 1). Several trends emerge from the peptide screen. At the $i+3$ position, steric size correlates with product enantioselectivity: the best ligands contain bulky residues at this position (e.g., **L7**, **L8**, **L20**, **L21**). The structural basis for selectivity at the $i-1$ position is less obvious. The best residues at the $i-1$ position include threonine, asparagine, and tryptophan, but selectivity drops significantly with the sterically demanding isoleucine (e.g., **L5**). Brief explorations of glutamate linkages (**L2**, **L17**, **L18**) or alternative carboxylate spacing (**L19**, **L22**) produced inferior catalysts. An intriguing aspect of this work is the variability in enantioselectivity between isomeric versions of a given *bis*-peptide catalyst. In certain cases both isomers of the *bis*-peptide catalysts exhibit comparable ee (e.g., 79% and 81% for **L8**), while for other ligands a pronounced difference is observed (7% and 80% for **L7**). Several α-diazoesters were examined for Si−H insertion using the optimized catalyst, Rh_2(**L21**)$_2$-isoB. All 3- and 4-substituted aryl substrates reacted to form the product with 90−99% ee (Table 1). Ortho substitution has a deleterious effect on selectivity (entries 8−9). Allylsilanes are important chiral intermediates, and we were gratified to find that a vinyl-substituted diazo substrate could also be efficiently transformed into the corresponding allyl silane (entry 7). Selectivity was lower for an alkyl-substituted substrate (entry 10).

Table 1. Asymmetric Insertion of Diazoacetates into Si−H Bonds



entry	starting material	product	ee[a] (%)	yield[b] (%)
1		**1b**	92	85
2		**2b**	95	86
3		**3b**	93	80
4		**4b**	99	72
5		**5b**	94	88
6		**6b**	99	90
7		**7b**	90[c]	97[d]
8		**8b**	49	51
9		**9b**	20	n.d.[e]
10		**10b**	64[f]	n.d.[e]

[a] The absolute configuration of **1b** was established by comparison of optical rotation to published data; that of other products is assumed by analogy. [b] Isolated yields of pure material. [c] The ee was determined after reduction to the alcohol. [d] Yield based on ^{1}H NMR relative to an internal standard. [e] n.d. = Not determined. [f] The silane used was Ph_2MeSiH.

In conclusion, we demonstrate a strategy to utilize natural polypeptide ligands in the development of chiral dirhodium catalysts. Starting from a relatively poor initial "hit" of 45% ee, the power of parallel automated peptide synthesis allowed us to quickly arrive at an effective catalyst. The combined efficiency of peptide libraries and facile dirhodium complexation should prove valuable in the discovery of selective catalytic transformations.

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Supporting Information Available: Experimental details, spectral data for insertion products, and characterization data for metallopeptides. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) We have not assigned parallel or antiparallel structures. The labeling of "A" and "B" isomers is arbitrary based on HPLC elution time.
(12) We find that ee improves modestly with decreasing temperature, but the metallopeptide becomes insoluble below −35 °C. We have not conducted a broad investigation of solvent effects, partly due to solubility limitations.

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