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Parallel Approach to Selective Catalysts for Palladium-Catalyzed Desymmetrization of 2,4-Cyclopentenediol

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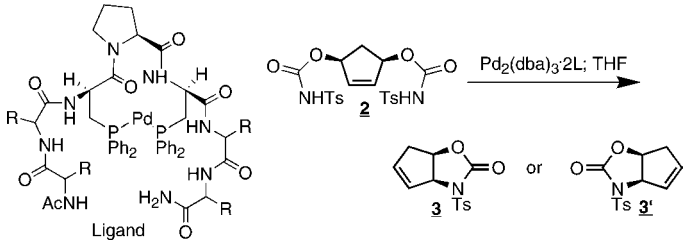
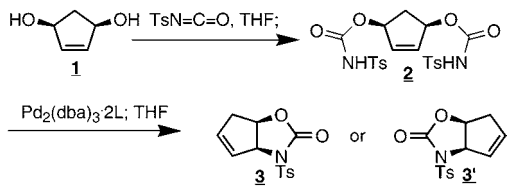
ABSTRACT



Work toward the development of a bis-phosphine ligand system for the palladium-catalyzed desymmetrization of meso-diols is reported. A parallel approach using phosphine-containing amino acids and a "representational search" was taken to find a polymer-supported catalyst system. The selectivities reported are comparable to many other polymer-bound asymmetric catalysts.

The palladium-catalyzed desymmetrization of meso-diols is formally an intramolecular allylic substitution reaction of a meso-substrate with two enantiotopic leaving groups (Scheme 1). The reaction was developed in the Trost lab and has been

Scheme 1



successfully used in the synthesis of natural products.[1−7] Other than the Trost work, there have only been a select number of successful attempts to perform this reaction in an asymmetric manner.[8−10] Given this, we decided to develop a selective catalyst for this transformation using the parallel synthesis of prospective ligands. In this paper, we report the development of a support-bound ligand that provides the desymmetrization product with moderate to good selectivity.

While this reaction is an example of an asymmetric palladium-catalyzed allyl substitution, it differs from standard

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intermolecular examples in the enantiodetermining step. In typical palladium-catalyzed intermolecular asymmetric allylations, the enantioselectivity is set by the attack of the nucleophile on one of two different carbons of a palladium allyl complex (**4**).[11−18] In this reaction, the asymmetric induction takes place during the formation of the allylic complex when one of the two enantiotopic carbamates is lost to form the intermediate palladium complex (**7** vs **7′**). The subsequent attack of the internal nucleophile provides the product. This fundamental difference in the origin of selectivity appeared to provide an excellent test for the ability to use a parallel approach in the development of selective catalysts. Such an approach has been taken for a select number of reactions.[19−28]

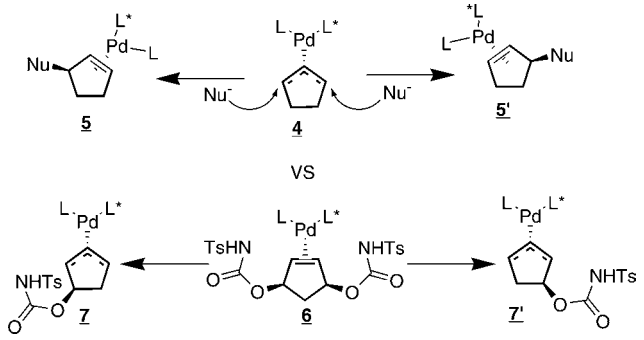

Figure 1. Two different enantiodeterming steps.

In previous work on palladium-catalyzed addition of malonate to cyclic allyl acetates, we have found that phosphine-containing β-turn peptide motifs can be useful in selective palladium-catalyzed allylations.[29] Initially, we attempted to catalyze the desymmetrization reaction with palladium complexes based on this type of structural format. A sequence that had been quite selective in the intermolecular addition, Ac-D-Phg-L-Pps-Pro-D-Val-L-Pps-D-Tle-[support] (Pps represents an amino acid containing diphenylphosphine in its side chain), was used to optimize the reaction conditions, including palladium source, solvent, and additive. The reaction conditions that ultimately gave the best selectivity with this ligand proved to be $Pd_2(dba)_2 \cdot CHCl_3$ as the palladium source, THF as the solvent, and tetrabutylammonium fluoride (TBAF) added as a base (37% ee). Examination of other sequences designed to be β-turns resulted in similar selectivities.

On the basis of the moderate selectivities obtained with turn motifs, sequences that were not expected to form a particular secondary structure were tested. A sequence with the two phosphine-containing amino acids separated by a single amino acid resulted in selectivity equal to that of the best β-turn formats. This is different than the case of intermolecular allylations, which appear to require a stable secondary structure for high selectivity. It was decided to attempt to optimize the [Pps-(amino acid)-Pps] motif for this reaction.

With the assumption that the most significant residue in such a sequence would be the one between the two phosphine-containing amino acids, seven ligands, where this amino acid was varied, were synthesized and screened. A significant difference between proline and the other amino acids tested was observed, with proline giving 47% ee (Figure 2). While replacement of D-Phe for L-Phe and D-Val for L-Val had little effect on the selectivity, replacement of L-Pro with D-Pro resulted in a significant decrease in selectivity. On the basis of these results, the Pps-Pro-Pps-Gly tetramer was accepted as the scaffold of choice for future optimization.

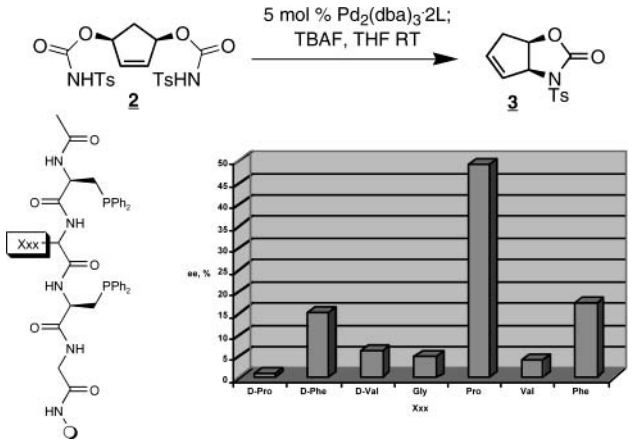

Figure 2.

To provide additional sites of diversity, two amino acids where attached to each end of the tetramer. The general structure of the template is shown in Figure 3. This structure

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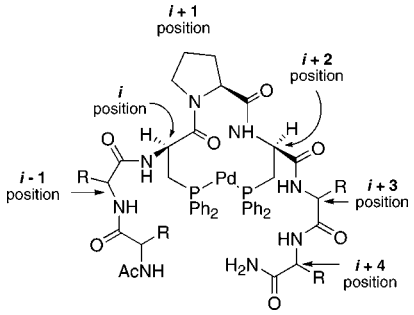

Figure 3. Positions are numbered on the basis of β-turn peptides. We currently do not know the secondary structure of these peptides.

possesses six positions at which it can be optimized. Changes in the *i* and *i* + *2* positions can be made by using different phosphorus-containing amino acids. In the study reported here, this site was held constant. Commercially available amino acids were used to modify the other positions. Since proline appears to be the optimal type of amino acid in position *i* + 1, a variety of proline derivatives were tested in that position.

To avoid the screening of all possible ligands, a "representational search", where each of the six positions was successively optimized by varying amino acids at a given position while keeping all other subunits constant, was employed.[30] After the optimal amino acid was found for a particular position, it was held constant in the subsequent experiments. The advantage of such an approach is that a much smaller number of ligands need to be tested. The disadvantage is that the "best" ligand identified could be a local maximum. Possible refinements of this strategy would be to choose a different starting point, changing the order of the optimization or after going through all positions going back to the first one and trying to optimize it again.

The *i* − 1 and *i* + 4 positions were the next to be tuned. To avoid screening through both L- and D-isomers of each amino acid, three peptides were prepared. One, Ac-Phe-Pps-Pro-Pps-Gly-Phe-[support], had L-Phe in the *i* − 1 and *i* + 4 positions; another, Ac-D-Phe-Pps-Pro-Pps-Gly-D-Phe-[support], had D-Phe, and a third, Ac-Gly-Pps-Pro-Pps-Gly-Gly-[support], had Gly in those positions. The peptide with L-Phe afforded 50% ee, and the peptide with Gly gave 54% ee. Both of these selectivities were lower than the 61% ee obtained with D-Phe in these positions. Because of this result, only D-amino acids were tested in the *i* − 1 and *i* + 4 positions.

D-Valine was chosen as a fixed *i* − 1 subunit, and different amino acids were tested in the *i* + 4 position (Figure 4). Out of 24 amino acids, D-leucine gave the highest ee (68%). Alanine and cyclohexylalanine were the second best amino acids, affording 65% ee. Only methionine and histidine afforded selectivities below 40% ee.

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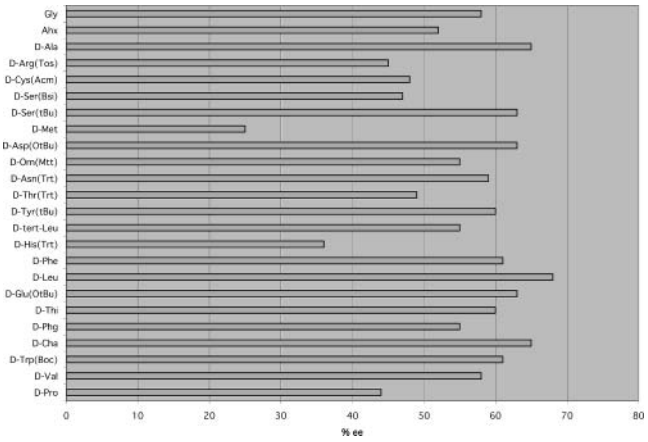


Figure 4. Optimization in the *i* + 4 position of [D-Val-Pps-Pro-Pps-Gly-[*i* + 4]-support]. (a) All reactions where run at rt overnight. In select cases, isolated yields of the products where obtained (60−70%). Selectivities were determined by HPLC on Chiralpak AD, using 2-propanol/hexane = 1:5, 1.0 mL/min, UV 204 nm. On the basis of repetitive runs using different samples of the same peptide sequence, the selectivities have been found to vary by ±2%.

It is interesting to note that this reaction appears to be more sensitive to substitution of various amino acids than our previous systems based on β-turn structures. In those systems substitutions at the ends of the peptides did not have a significant effect on the catalyst's selectivity. With a few exceptions, it appears that amino acids with sterically bulky side chains give the best results. However *tert*-Leu afforded 55% ee vs 68% ee obtained with Leu. In the cases of extremely large side chains, the catalyst's structure may be more significantly altered, leading to a decrease in selectivity.

After finding the optimal amino acids for the *i* + 4 position, with D-Val in that position, the same 24 amino acids were tested in the *i* − 1 position (Figure 5). Interestingly, the substitution in this position caused a much smaller fluctuation in the selectivity. Three amino acids, D-Asp-(OtBu), D-Phg, and D-Val, afforded 68% ee.

Again, methionine and histidine provided the lowest ees, which is probably due to some negative interaction between the metal and these amino acids' side chains. All other acids afforded selectivities between 61 and 68% ee. Surprisingly, even D-Pro in this position gave good selectivity (65% ee).

The best peptide in this library was removed from the support and tested for its ability to perform selective catalysis. Catalysis with the palladium complex of Ac-Val-D-Pps-D-Pro-D-Pps-Gly-Leu-NHMe in solution provided the same selectivity (68% ee) as its enantiomer while attached to a solid support. As expected, the opposite enantiomer was the major product.

In what might be considered a second-generation optimization, seven different amino acids were checked as alternatives to proline in the *i* + 1 position. Three commercially available (Pip, Oic, Tic) cyclic amino acids and four derivatives of hydroxyproline were examined (Scheme 2).

Octahydroindole-2-carboxylic acid (Oic) gave the best selectivity (76% ee), and MOM-protected *cis*-hydroxyproline

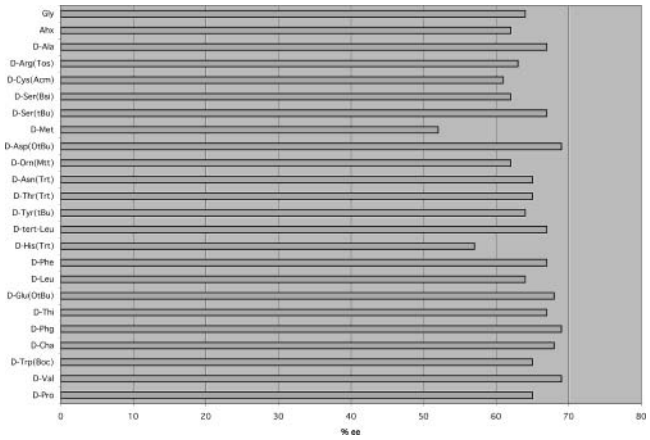


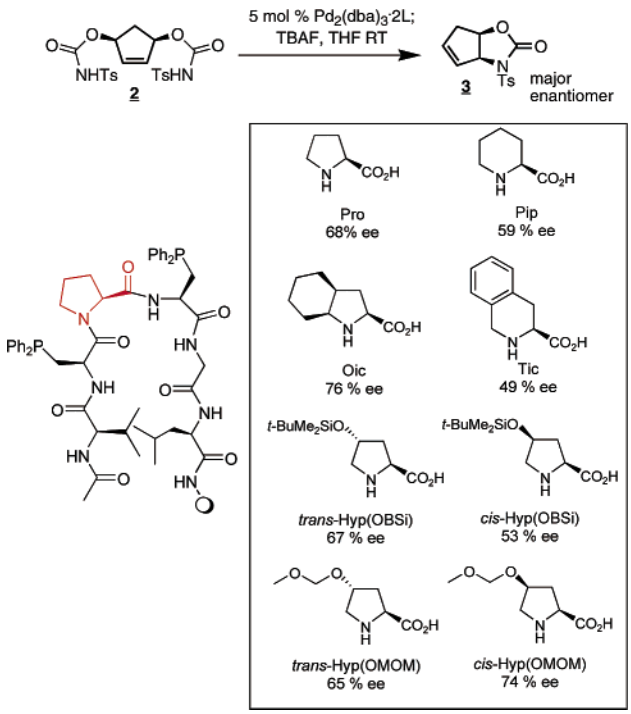
Figure 5. Optimization in the $i - 1$ position [Ac-[$i - 1$]-Pps-Pro-Pps-Gly-D-Leu-support. (a) All reactions where run at rt overnight. In select cases, isolated yields of the products where obtained (60−70%). Selectivities were determined by HPLC on Chiralpak AD, using 2-propanol/hexane = 1:5, 1.0 mL/min, UV 204 nm. Based on repetitive runs using different samples of the same peptide sequence the selectivities have been found to very by ± 2%.

gave the second highest (74% ee). In the case of *cis*-hydroxyproline, TBDMS-protected hydroxyl group caused a 21% drop in ee compared to MOM. Both derivatives of *trans*-Hyp afforded results similar to proline, while the six-member analogues, Pip and Tic, provided considerably poorer selectivities.

In the last set of experiments, the importance of glycine in the $i + 3$ position was examined [Ac-D-Val-Pps-Pro-Pps-**Gly**-D-Val-support]. Four new peptides were synthesized, with alanine and phenylalanine replacing Gly. All substitutions had a detrimental effect on the selectivity. Substitution with the L-isomers afforded only a slight decrease in selectivity, but the members containing D-isomers gave significantly lower selectivity.

At this point, the representational search was completed. The new scaffold was found through screening 75 ligands, with Ac-D-Val-Pps-Oic-Pps-Gly-D-Leu-NH-peptide identified as the most selective catalyst for the desymmetrization of **1**. While good correlation was observed between catalysis with

Scheme 2



the complex immobilized on support and with it in solution, we are continuing to study these ligands in solution to optimize the reaction conditions for homogeneous catalysts. To determine the origin of selectivity, the structure of the ligand metal complex is also being examined.

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Supporting Information Available: Spectral data for all new compounds, experimental procedures, and tables or selectivities of each library. This material is available free of charge via the Internet at http://pubs.acs.org.

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