Mining Sequence Space for Asymmetric Aminocatalysis: *N*-Terminal Prolyl-Peptides Efficiently Catalyze Enantioselective Aldol and Michael Reactions

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Abstract: *N*-Terminal prolyl-peptides efficiently catalyze asymmetric aldol and Michael reactions between acetone and *p*-nitrobenzaldehyde or β-nitrostyrene, respectively.

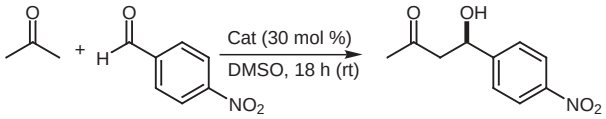
Key words: organocatalysis, enamine catalysis, aminocatalysis, peptides

Enantioselective organocatalysis with amines, also termed asymmetric aminocatalysis, is a useful strategy for several important carbonyl reactions.[2] Among the catalysts studied so far, the amino acid proline has arguably been the most successful in enamine involving reactions.[3–6] Its popularity is based on the efficiency and stereoselectivity often encountered in proline-catalyzed reactions and on its inexpensive and non-toxic nature. Despite these attractive features, there is still room for improvement. For example, potentially useful donors such as acetaldehyde[7] and acetophenone[8] can not readily be used, stereoselectivities and yields can be sub-optimal, and α-unbranched aldehydes are notorious acceptors in proline-catalyzed aldol reactions.[4c] In addition, there are several interesting enamine involving reactions that can not be catalyzed by proline. To address these shortcomings, a readily available and diversifiable substance-class from which improved enamine catalysts could be selected is highly desirable. Here we show for the first time that *N*-terminal prolyl-peptides efficiently catalyze asymmetric aldol and Michael reactions.

Pioneered by Miller[9] and Jacobsen[10] catalytic peptides and peptide-like molecules were recently introduced as asymmetrc catalysts.[11] Their structural and chemical diversity, accessibility, and inherent chirality could make them ideal asymmetric organocatalysts for a variety of reactions. We speculated that the infinite sequence space of *N*-terminal prolyl peptides might be a good source for the discovery of novel enamine catalysts. To test this hypothesis we have studied di- and tripeptide-catalyzed aldol reactions of acetone with *p*-nitrobenzaldehyde. To our delight, we found all tested peptides to show efficient catalytic activity producing the aldol product in good yields (62–90%) and enantioselectivities (31–77%, Table 1). These results are particularly remarkable in light of the observation that catalysis by proline amide is much less efficient than that by proline, and that it provides the product in only 20% ee.

Next, we found the same peptides to also catalyze direct asymmetric Michael reactions between acetone and *trans*-β-nitrostyrene with good results (Table 2). Here, enantioselectivities of up to 31% were observed. Though still modest, these enantioselectivities constitute a significant improvement over the 7% ee realized in the corresponding proline-catalyzed reaction.

Table 1 Peptide-Catalyzed Aldol Reactions



Entry	Catalyst	Yield (%)[a]	ee (%)[b]
1	Pro-OH	68	76
2	Pro-Ala	90	70
3	Pro-Trp	77	65
4	Pro-Asp	75	74
5	Pro-Glu	72	68
6	Pro-Val	89	70
7	Pro-Arg	91	31
8	Pro-Ser	87	77
9	Pro-Lys·HCl	62	66
10	Pro-Gly-Gly	68	53
11	Pro-His-Ala	85	56

[a] Yields were determined by preparative TLC. As the major side product the aldol condensation product has been identified.
[b] Enantiomeric excess (ee) values were determined from chiral stationary-phase HPLC analysis.

In conclusion we show that *N*-terminal prolyl peptides are promising asymmetric aminocatalysts. Although only modest enhancements compared to proline catalysis were realized so far, our results suggest that screening larger libraries of *N*-terminal prolyl peptides could provide effective catalysts with improved enantioselectivities and yields.[12] In addition we expect *N*-terminal prolyl peptides

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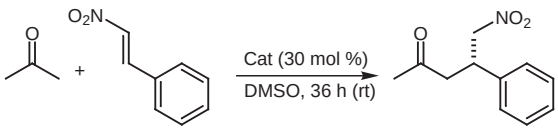
Table 2 Peptide-Catalyzed Michael Reactions



Entry	Catalyst	Yield (%)[a]	ee (%)[b]
1	Pro-OH	97	7
2	Pro-Ala	71	5
3	Pro-Trp	68	0
4	Pro-Asp	75	3
5	Pro-Glu	91	8
6	Pro-Val	65	31
7	Pro-Arg	65	19
8	Pro-Ser	81	8
9	Pro-Lys·HCl	66	8
10	Pro-Gly-Gly	79	10
11	Pro-His-Ala	70	7

[a] Yields were determined by preparative TLC. No side products have been identified.
[b] Enantiomeric excess (ee) values were determined from chiral stationary-phase HPLC analysis.

to become useful catalysts for a variety of other important aminocatalytic transformations.

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