

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

Harry J. Martin, Benjamin List*¹

Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA
Fax +1(858)7847028; E-mail: blist@scripps.edu.

Received 28 February 2003

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

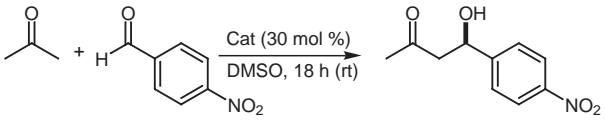
Enantioselective organocatalysis with amines, also termed asymmetric aminocatalysis, is a useful strategy for several important carbonyl reactions.² Among the catalysts studied so far, the amino acid proline has arguably been the most successful in enamine involving reactions.^{3–6} Its popularity is 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 acetaldehyde⁷ and acetophenone⁸ 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 Miller⁹ and Jacobsen¹⁰ catalytic peptides and peptide-like molecules were recently introduced as asymmetric 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

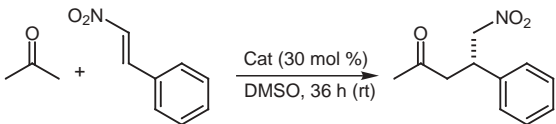


Entry	Catalyst	Yield (%) ^a	ee (%) ^b
1	Pro-OH	68	76
2	Pro-Ala	90	70
3	Pro-Trp	77	65
4	Pro-Asp	75	74
5	Pro-Glu	72	68
6	Pro-Val	89	70
7	Pro-Arg	91	31
8	Pro-Ser	87	77
9	Pro-Lys-HCl	62	66
10	Pro-Gly-Gly	68	53
11	Pro-His-Ala	85	56

^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

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.

Acknowledgment

Support by the NIH (GM-63914) is gratefully acknowledged. We thank William T. Biller for technical assistance.

References

- (1) New Address: Max-Planck-Institut für Kohlenforschung, 45470 Mülheim an der Ruhr, Germany.
E-mail: list@mpi-muelheim-mpg.de

- (2) For some recent reviews and highlights, see: (a) Gröger, H.; Wilken, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 529. (b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726. (c) List, B. *Synlett* **2001**, 1675. (d) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (e) List, B. *Tetrahedron* **2002**, *58*, 5572. (f) Borman, S. *Chem. Eng. News* **2002**, *80*(50), 35. (g) Movassaghi, M.; Jacobsen, E. N. *Science* **2003**, *298*, 1904. (h) Paraskar, A. S. *Synlett* **2003**, 582.
- (3) (a) Hajos, Z. G.; Parrish, D. R. German Patent DE 2102623, **1971**. (b) Eder, U.; Sauer, G.; Wiechert, R. German Patent DE 2014757, **1971**. (c) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (d) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (e) Related enantiogroup-differentiating aldol cyclodehydrations have been described, see: Agami, C.; Platzer, N.; Sevestre, H. *Bull. Soc. Chim. Fr.* **1987**, *2*, 358.
- (4) For the first proline-catalyzed asymmetric intermolecular aldol, Mannich-, Michael-, and α -amination reactions, see (a) List, B.; Lerner, R. A.; Barbas, C. F. III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (c) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (d) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (e) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (f) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. (g) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656.
- (5) (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (b) Cordova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F. III *J. Am. Chem. Soc.* **2002**, *124*, 1866. (c) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620. (d) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790. (e) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 661. (f) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245.
- (6) For pioneering experiments on enantioselective iminium catalysis, see: Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192; and references therein.
- (7) Córdoba, A.; Notz, W.; Barbas, C. F. III *J. Org. Chem.* **2002**, *67*, 301.
- (8) For the only exception, see: Enders, D.; Seki, A. *Synlett* **2002**, 26.
- (9) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J. Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638.
- (10) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279.
- (11) For the use of peptide-derived ligands in asymmetric transition metal catalysis, also see: Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456; and references therein.
- (12) After this manuscript has been accepted for publication, related results were reported by: Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445.