ORGANIC LETTERS

2003
Vol. 5, No. 20
3741−3743

Dual Catalyst Control in the Amino Acid-Peptide-Catalyzed Enantioselective Baylis–Hillman Reaction

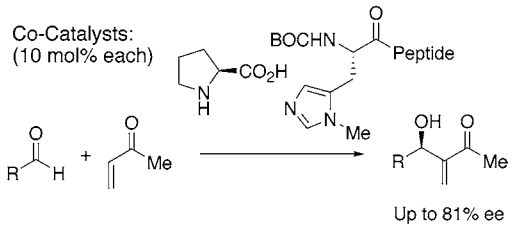
Jason E. Imbriglio, Melissa M. Vasbinder, and Scott J. Miller*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

scott.miller.1@bc.edu

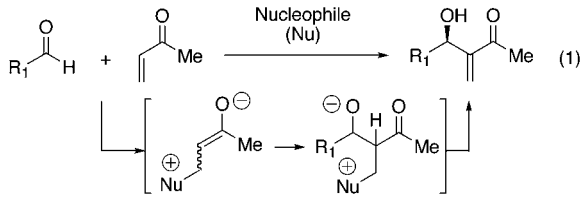
Received August 4, 2003

ABSTRACT



Nucleophile-loaded peptides and proline have been found to function synergistically as cocatalysts for the asymmetric ketone-based Baylis–Hillman reaction. Although neither compound is effective independently in terms of rate or enantioselectivity, their combination leads to catalysis where enantioselectivities up to 81% have been observed.

Enantioselective catalysts are very often composed of unique molecular entities that chaperone substrates through a given reaction coordinate. At the same time, a host of features in addition to the catalyst structure can contribute to product enantioselectivity, including additive effects.[1] Given that amino acids and peptides provide extensive opportunities for catalyst tuning, we sought to explore the possibility of synergistic effects between two distinct cocatalytic entities. The methyl vinyl ketone (MVK)-based Baylis−Hillman (BH) reaction (eq 1), a current subject of extensive study in asymmetric catalysis,[2] provides an opportunity to explore this concept. The accepted mechanism is multistep and provides multiple opportunities for catalytic intervention. In addition, the state of the art for the MVK-based Baylis−Hillman reaction reflects maximum ee's in the 50% range such that there is an opportunity to observe improvements.[3] Among the exciting recent advances is the modified cinchona alkaloid catalyst of Hatakeyama for the ester-based BH reaction.[4] In addition, Shi and Jiang have documented that the Hatakeyama catalyst,[5] in combination with proline[6] as a cocatalyst, provides ee values of up to 31% for the MVK-based BH reaction.



We have been studying peptide-based nucleophiles that enable new enantioselective processes.[7] Given the extensive diversity of structure and function available to peptides, we

(1) Vogl, E. M.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570−1577.

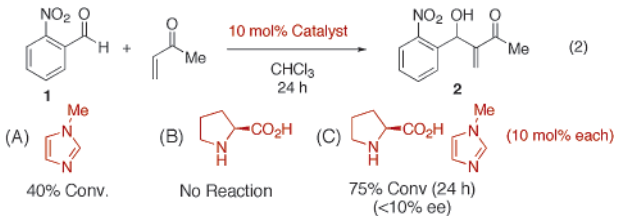
(2) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811−891. (b) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049−3052.

(3) (a) Walsh, L. M.; Winn, C. L.; Goodman, J. M. *Tetrahedron Lett.* **2002**, *43*, 8219−8222. (b) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241−1244. (c) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533−2534. (This paper includes a report of 71% ee for a Baylis−Hillman reaction employing ethyl vinyl ketone.)

(4) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219−10220.

10.1021/ol035466b CCC: $25.00
Published on Web 09/06/2003

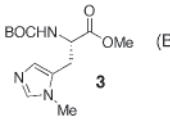
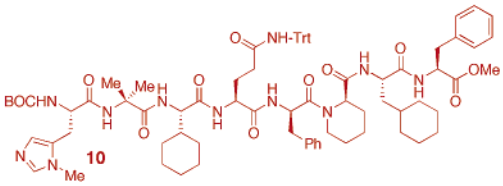
sought to extend the scope of these catalysts to enantioselective C−C bond formation. In particular, the possibility for peptides to form noncovalent interactions with cocatalysts seemed particularly intriguing. At the outset, in analogy to Shi, we established that the combination of a nucleophilic catalyst and proline could provide effective cocatalysis. As shown in eq 2 (condition A), *N*-methylimidazole (NMI, 10 mol %) in the absence of proline catalyzes a sluggish reaction between MVK and aldehyde **1** (40% conv, 24 h). The use of proline alone (condition B) provides no product in the same time window. Yet, when the two are employed together (condition C), an approximate doubling of the rate occurs (75% conv, 24 h). Notably, product **2** is nearly racemic, indicating the influence of the L-Pro chirality to be minimal.[8]



In contrast, exchange of NMI for π-(Me)His (Pmh)-containing peptides produces sharply different results (Table 1). When Pmh-derivative **3** is employed as a cocatalyst with Pro, product **2** is produced with 19% ee (entry 1). Furthermore, extending the length of the peptide-cocatalyst leads to increases in enantioselectivity.[9] Whereas dipeptide **4**, tripeptide **5**, and tetrapeptide **6** give the product with similar selectivity (33%, 33%, and 40% ee, respectively; entries 2−4), pentamer **7**, hexamer **8**, and heptamer **9** produce alcohol **2** with 47%, 61%, and 73% ee, respectively (entries 5−7). The optimal peptide among those evaluated is octamer **10**, which delivers product **2** with 78% ee (89:11 enantiomer ratio). The roughly linear correlation between chain length and product ee prompted us to examine 9-mer **11** and 10-mer **12**. Interestingly, neither leads to an increase in selectivity. However, we emphasize that none of the catalysts of a given peptide chain length is fully optimized. We also note that control experiments documented that each of the peptides, in the absence of proline, functions as a poor catalyst, affording low yields and selectivities (<10% ee) in each of the cases we examined.

With a cocatalyst combination (**10**/Pro) on hand that provided a result of 78% ee, we sought to examine whether the results would be highly specific for the unique substrate upon which the screens were performed. Table 2 shows the

Table 1. Catalyst Screen for the MVK-Based BH Reaction with Aldehyde **1**[a]

entry[b]		ee[c]
1	 (BOC-Pmh-OMe)	19%
2	BOC-Pmh-Aib-OMe (**4**)	33%
3	BOC-Pmh-Aib-Phe-OMe (**5**)	33%
4	BOC-Pmh-Aib-Phe-DPhe-OMe (**6**)	40%
5	BOC-Pmh-Aib-Cha-hPhe-DPhe-OMe (**7**)	47%
6	BOC-Pmh-Aib-Chg-Gln(trt)-DPhe-Phe-OMe (**8**)	61%
7	BOC-Pmh-Aib-Chg-Gln(trt)-DPhe-(BOC)Trp-Phe-OMe (**9**)	73%
8		78%
9	BOC-Pmh-Aib-Chg-Gln(trt)-DPhe-DPip-Cha-Phe-Phe-OMe (**11**)	75%
10	BOC-Pmh-Aib-Chg-Gln(trt)-DPhe-DPip-Cha-Val-(BOC)Trp-Phe-OMe (**12**)	74%

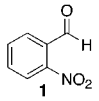
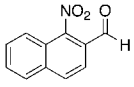
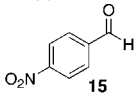
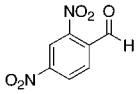
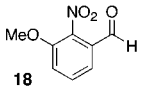
[a] All reactions were conducted at 25 °C. [b] All reactions proceeded to >75% conversion within 16 h as determined by ^{1}H NMR (400 MHz). [c] Determined by chiral HPLC. Reported ee values are the average of 2 runs. See Supporting Information for details.

results of this substrate screen. A range of aromatic aldehydes were explored with comparable results. Nitronaphthaldehyde **14** and *p*-nitrobenzaldehyde **15** participate in the reaction with 73% and 69% ee, respectively (entries 2 and 3). Furaldehyde is converted to the BH-product with 63% ee (entry 4).[10] Dinitrobenzaldehyde **17** undergoes reaction to afford product with 63% ee (entry 5). 3-Methoxy-2-nitrobenzaldehyde (**18**) undergoes the reaction to deliver the BH product with 81% ee (entry 6). *o*-Trifluoromethylbenzaldehyde (**19**) affords the product with 71% ee (entry 7).

Given that the NMI-Pro cocatalyst system does not afford appreciable enantioselectivity for the parent reaction, the observed asymmetric catalysis may indeed be due to the specific interactions between Pro and the peptide-based nucleophile. To probe the nature of the potential interaction, we performed parallel cocatalytic reactions with peptide **10** and the two enantiomers of proline (Scheme 1). "Matched" and "mismatched" pairs of cocatalysts are readily identified. Whereas the combination of L-Pro and **10** gives product (*R*)-**2** with 78% ee, the D-Pro-**10** combination produces (*S*)-**2**, with a reduced 39% ee. Furthermore, in the latter reaction, the opposite enantiomer of the BH product is the dominant isomer formed. *The enantiodivergence is of particular note, since it implies that it is the proline stereochemistry that dominates that of the peptide in the stereochemistry-*

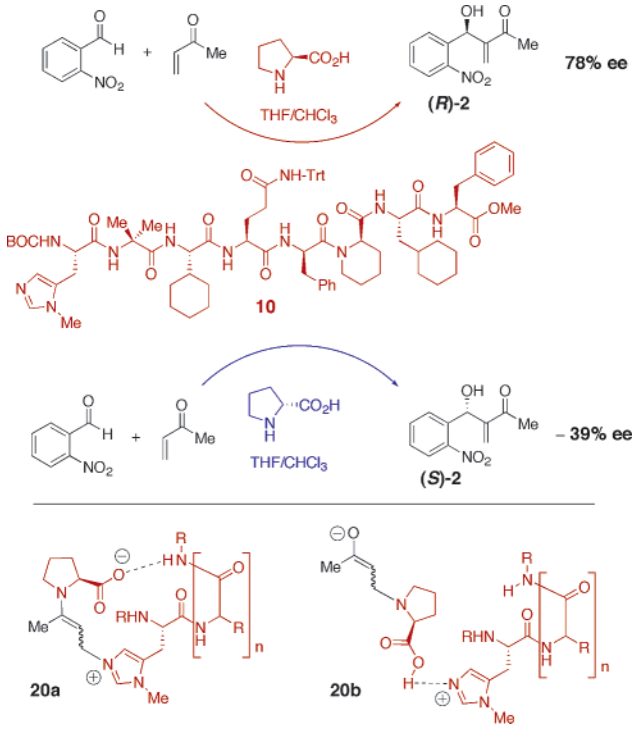
(5) Shi, M.; Jiang, J.-K. *Tetrahedron: Asymmetry* **2002**, *13*, 1941−1947.
(6) (a) List, B. *Tetrahedron* **2002**, *58*, 5573−5590. (b) Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904−1905.
(7) For example: (a) Acylation: Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496−6502. (b) Phosphorylation: Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 11653−11656. (c) Azidation: Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134−2136. (d) For a review, see: Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481−2495.
(8) Shi, M.; Jiang, J.-K.; Li, C.-Q. *Tetrahedron Lett.* **2002**, *43*, 127−130.
(9) Not all of the peptides screened are shown in Table 1. A representative set for each chain length was prepared.
(10) For the furaldehyde reaction, higher selectivities were observed in a toluene/$CHCl_3$ (2:1) solvent mixture.

Table 2. Substrate Screen for the BH Reaction with Cocatalyst **10**/Pro[a]

entry	substrate	yield[b]	ee[c]
1	 **1**	81%	78%
2	 **14**	92%	73%
3	 **15**	81%	69%
4	 **16**	>95%[d]	63%
5	 **17**	89%	63%
6	 **18**	88%	81%
7	 **19**	52%	71%

[a] All reactions were conducted at 25 °C. [b] Isolated yields after silica gel chromatography. [c] Determined by chiral HPLC. Reported ee values are the average of at least 2 runs. See SI for details. [d] Refers to conversion by ^{1}H NMR; isolated yield after catalytic hydrogenation of the olefin is comparable.

Scheme 1



determining step. Taken together, the experiment shows that the combination of L-Pro and peptide **10** provides a catalytic system that is clearly greater than the sum of its parts. The data also imply that a cohesive transition state assembly such as that depicted by structure **20a**, may be operative. The intermediacy of proline-derived enamines has been documented to provide a highly versatile template for asymmetric organocatalytic reactions.[11] On the other hand, two-catalyst transition states that involve a complex between the peptide and the proline−MVK conjugate addition product (**20b**) cannot be ruled out, although the details of structure for such a complex are unclear at this time. That either type of intermediate, or yet another alternative, may be tuned through peptide-based noncovalent interactions with cocatalysts could represent a general strategy for catalyst optimization. An exploration of the peptide conformations, for example, to elucidate the role of the helix-promoting residue Aib,[12] will be a key factor of these studies.

In summary, we have demonstrated that the combination of peptides and single amino acids as cocatalysts can lead to an effective scenario for the asymmetric catalytic Baylis−Hillman reaction. While the results herein remain below the current high standard for synthetic utility in catalytic asymmetric synthesis, they provide state of the art selectivities for the MVK-based BH reaction. In addition, the use of peptide-based nucleophiles in tandem with other catalysts may represent a general concept for asymmetric catalyst design. The exploration of this possibility in the specific context of the asymmetric BH, and in other contexts as well, is now underway in our laboratory.

Acknowledgment. This research is supported by the NSF (CHE-0236591). We also acknowledge Merck Research Laboratories and Pfizer Global Research for research support. S.J.M. is a Fellow of the Alfred P. Sloan Foundation and a Camille Dreyfus Teacher-Scholar.

Supporting Information Available: Experimental procedures and product characterization for all new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035466B

(11) (a) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16−17. (b) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475−2479, and references therein.

(12) (a) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131−3152. (b) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Biopolymers* **2001**, *60*, 396−419.