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# Amino acid-peptide-catalyzed enantioselective Morita–Baylis–Hillman reactions

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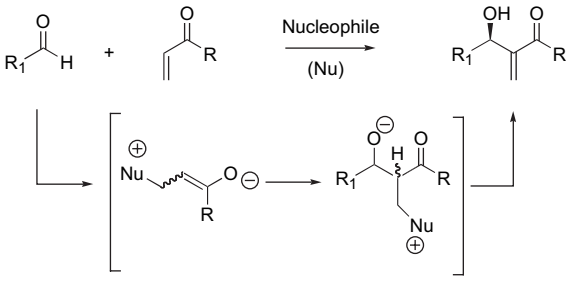
This article is dedicated to Professor David W. C. MacMillan on the occasion of his receiving the Tetrahedron Young Investigator Award

**Abstract**—Peptide-based catalysts in the presence of proline as co-catalyst have been found to catalyze the enantioselective ketone-based Morita–Baylis–Hillman reaction. The co-catalyst combination has afforded catalysis where enantioselectivities of up to 81% have been obtained.


## 1. Introduction

Our laboratory has been investigating peptide-based nucleophiles and bases that enable a number of new enantioselective processes, including catalytic asymmetric group transfers (acylation,[1] phosphorylation,[2] sulfinylation[3]), azidation,[4] and carbon–carbon bond-forming reactions.[5] Due to the diversity of function and structure that peptides provide,[6] we sought to extend the scope of these catalysts to the enantioselective Morita–Baylis–Hillman reaction.[5d] The Morita–Baylis–Hillman (MBH) reaction is a powerful carbon–carbon bond-forming reaction whose multi-step mechanism allows numerous possibilities for catalyst intervention (Eq. 1).[7] There have been many recent contributions to the enantioselective MBH reaction.[8] Hatakeyama and co-workers have developed cinchona alkaloid-based chiral nucleophiles for the acrylate ester-based MBH reaction in excellent enantioselectivities.[9] In addition, Shi and Jiang have reported the Hatakeyama's cinchona alkaloid catalyst, in the presence of proline as a co-catalyst, affords up to 31% ee for the methyl vinyl ketone (MVK)-based MBH reaction.[10] In an important control study, Shi and co-workers had shown that the co-catalyst system of proline and imidazole was effective for the production of MBH products, albeit with minimal ee.[11]



(1)

## 2. Results and discussion

We embarked upon studying the ketone-based Morita–Baylis–Hillman reaction by first screening a variety of substrates, including aldehydes and activated alkenes using *N*-methyl imidazole (NMI) as catalyst. In analogy to Shi and co-workers, we likewise were interested in determining whether NMI would serve as a catalyst in the MVK-Morita–Baylis–Hillman reaction. We reasoned if imidazole could catalyze the MBH reaction in the presence of L-proline, then NMI should also serve as a catalyst. Indeed, initial experiments demonstrated that NMI could catalyze the Morita–Baylis–Hillman reaction of MVK and 4-nitrobenzaldehyde (Fig. 1a), although only affording 40% conversion after 24 h. Using only proline as a catalyst afforded no reaction in the same time frame.[12] However, the combination of proline and NMI (10 mol % each) led to a near doubling of rate, yielding 75% conversion to the desired Morita–Baylis–Hillman product within 24 h (Fig. 1c). Interestingly, MBH product **1** was generated with <10% ee, implying that the chirality of L-proline did not lead to substantial ee in this case.

*Abbreviations*: Chg, α-cyclohexylglycine; Cha, 3-cyclohexylalanine; Phe, phenylalanine; Ala, alanine; Leu, leucine; Pro, proline; Trp(Boc), Boc protected tryptophan; HPhe, homophenylalanine; $Arg(Boc)_2$, di-Boc protected arginine; Gln(Trt), trityl protected glutamine; Pip, pipecolinic acid.

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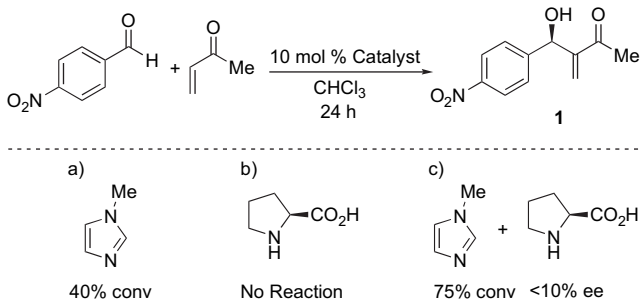



**Figure 1**. MBH reaction of 4-nitrobenzaldehyde and MVK in the presence of (a) NMI as catalyst, (b) Proline (Pro) as catalyst, and (c) co-catalyst combination of NMI and Pro.

Optimistic that replacing NMI with π-(methyl)histidine (Pmh)-containing peptides could afford an enantioselective reaction, we set out to screen peptide catalysts in the MVK-MBH reaction. We began screening libraries of peptides, which were available in our laboratory. These libraries consisted of tetrapeptides and octapeptides, which were biased toward β-hairpin scaffolds,[13] as well as pentapeptides, which were unbiased. The pentapeptides consisted of sequences, which contained Pmh at the *i*-position and at the *i*+4-position either an alanine or phenylalanine. Positions *i*+1 through *i*+3 were random sequences of 16 different amino acids.[14]

A selectivity profile from this initial catalyst screen of 105 peptides revealed a number of interesting trends.[15] Of the peptide catalysts screened, peptides, which provided up to 21% ee for the reaction of 4-nitrobenzaldehyde and MVK in the presence of proline were identified (Fig. 2).

Examining peptide catalysts which afforded 17–21% ee in the initial peptide screen offered useful comparisons. Three of the most active peptides screened showed homology within the peptide framework. Peptides **2**–**4** contained

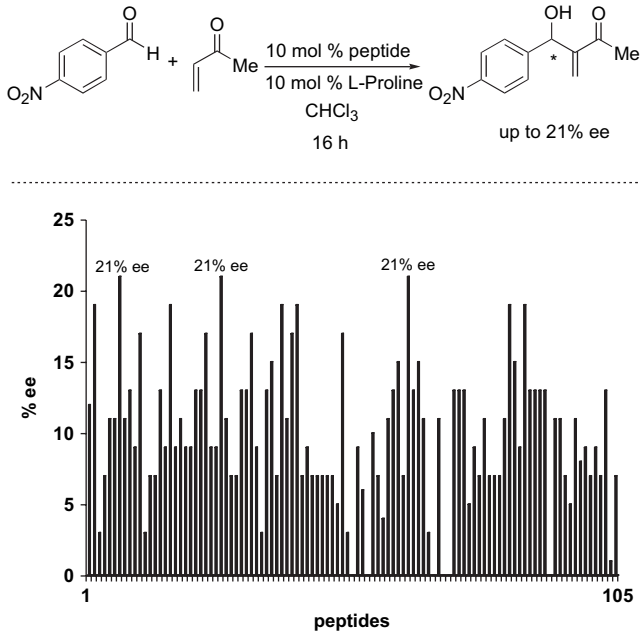



**Figure 2**. Initial screen of peptide catalysts in the MVK-MBH reaction.

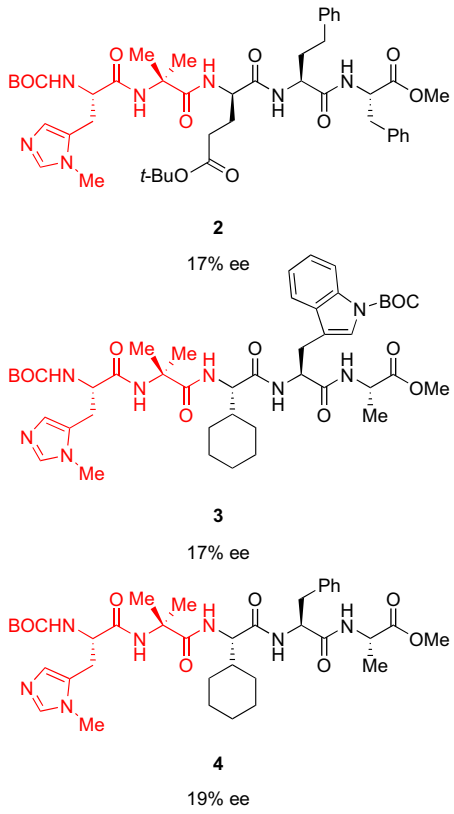


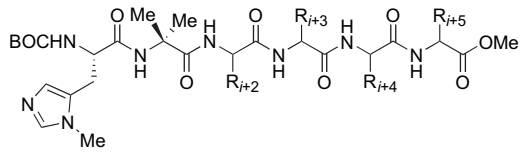

**Figure 3**. Selective pentapeptides which contain similar sequences.

Boc-Pmh at the *i*-position and Aib (α-aminoisobutyric acid) at the *i*+1-position, followed by the rest of the peptide sequence (Fig. 3).[16]

Based on the trends apparent within the peptide sequences of catalysts **2**–**4**, we speculated that the information embedded within the residues of these peptides would lead to an improved peptide catalyst. Thus, we began exploring the structure–activity relationship (SAR) of each position of peptides **3** and **4**.[17] Capitalizing on the Boc-Pmh-Aib sequence specificity at the N-terminus of the peptide, we made single point mutations on the peptide. We immediately discovered upon synthesizing modified catalysts that different peptide sequences could lead to higher ee, including 57% ee in the reaction of 2-nitrobenzaldehyde with MVK in the presence of proline (Fig. 4).[18] (At this stage, we began a parallel screen of both the 2- and 4-substituted nitrobenzaldehyde substrates.) Peptide **6**, with Cha at the *i*+2-position, yields 57% ee in the MBH product; peptide **5** resulted in 45% ee. Stereochemical modifications within the peptide sequence also proved to have a significant effect on the enantioselectivity. For example, peptide **7**, with D-Ala at the *i*+2-position, delivers reduced selectivity (23% ee).

We were also curious whether increasing the peptide chain length would perturb selectivity. To this end, we synthesized peptides of variable chain length. Hexamers **8** and **9** led to increased enantioselectivity (Fig. 4, peptide **8**, 47% ee and peptide **9**, 49% ee; cf. peptide **5**, 45% ee).

At this stage, we had observed that both residue identity and chain length were determinants of reaction enantioselectivity.



| Peptide | $R_{i+2}$ | $R_{i+3}$ | $R_{i+4}$ | $R_{i+5}$ | %ee |
|---|---|---|---|---|---|
| **5** | Chg | Phe | D-Phe | - | 45 |
| **6** | Cha | Phe | D-Phe | - | 57 |
| **7** | D-Ala | Phe | D-Phe | - | 23 |
| **8** | Chg | Phe | D-Phe | D-Phe | 47 |
| **9** | Chg | Phe | D-Phe | Phe | 49 |

**Figure 4**. Preliminary SAR based on hit pentapeptide sequences.

Therefore, we sought a method to rapidly screen the catalysts. A more combinatorial approach to the synthesis of new peptides was desired.[19] A 42-membered directed library[20] of hexapeptides was synthesized based on peptides **8** and **9**. The focused library incorporated 20 unique amino acids into the *i*+1 through *i*+4 positions of the hexamer sequence.[21] The amino acids that were used are listed in the abbreviations on the first page of the article.

The 42 peptides, which were synthesized in the library were then screened in the MBH reaction. The peptide selectivities ranged from 25 to 61% ee in the reaction of 2-nitrobenzaldehyde and MVK in the presence of L-proline and peptide catalyst (10 mol % each) at room temperature. Peptides **10** and **11** indeed provided a boost in enantioselectivity, with catalyst **10** affording 60% ee and peptide **11** yielding MBH product in 61% ee (Fig. 5).

At this stage, we wondered whether further extension of the peptide chain would continue to afford more selective catalysts. Because peptide **11** had afforded the highest level of selectivity in the MBH reaction, we took this sequence and continued to optimize in an iterative manner.[22] Representative amino acids were evaluated at the *i*+5, *i*+6, and *i*+7 positions. While aliphatic, aromatic, branched aliphatic, and other amino acids were inserted at each position, it is important to note that at no position was a comprehensive set of residues explored. Thus, we remain uncertain as to whether the optimum sequence has been discovered. Nevertheless, our observations indicated that heptameric and octameric sequences appeared to increase the enantioselectivity of the reaction. However, upon reaching the decapeptide stage, the enantioselectivity appeared to plateau (Table 1).[23] It is important to underscore further that at no sequence length was a comprehensive exploration of residues explored. Thus, although peptide **18** emerged as that exhibiting maximum enantioselectivity (78% ee), it may be that superior sequences may be found at shorter chain lengths, or longer sequences. Efficient methodology for a comprehensive survey of residues at a given chain length is, at this time, elusive.[24]

With a co-catalyst combination of octapeptide **18**-proline available that afforded MBH product **1** in 78% ee, we wished

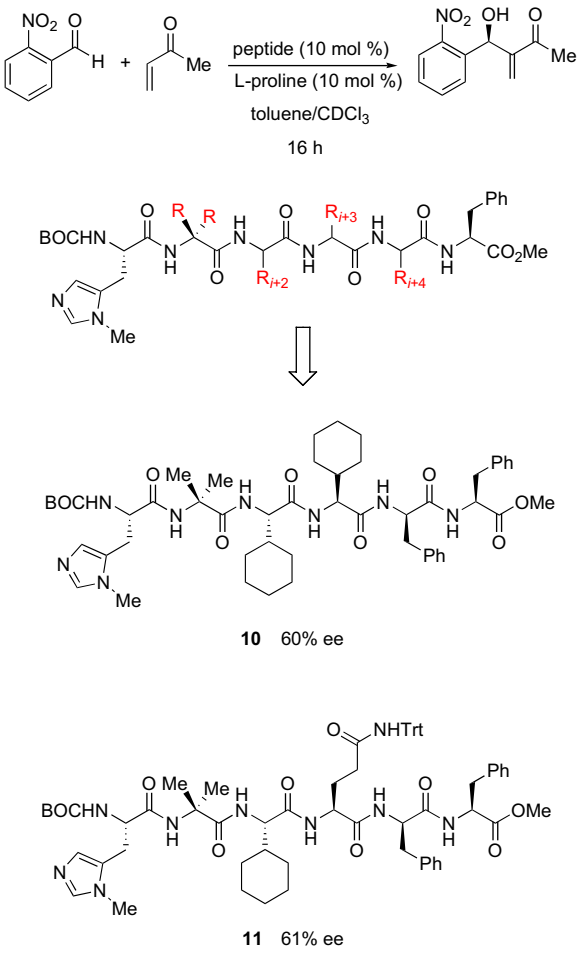
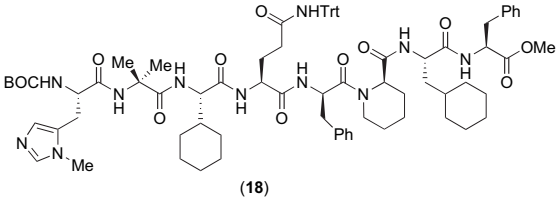



**Figure 5**. Directed library design for the synthesis of 42 new hexapeptides.

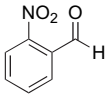
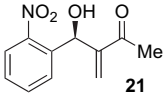
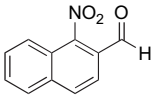
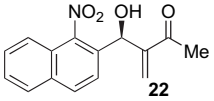
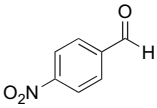
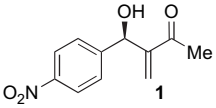
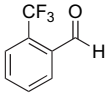
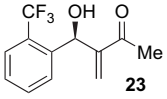
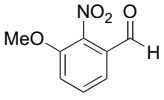
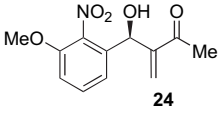
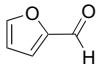
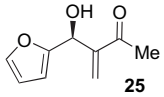
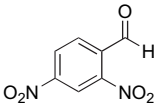
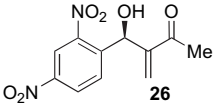
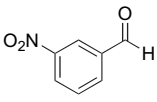
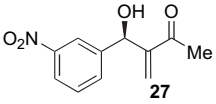
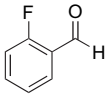
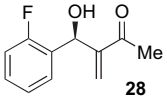
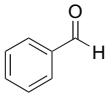
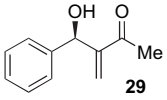
**Table 1**. Catalyst screen for the MVK-MBH reaction with 2-nitrobenzaldehyde[a]

| Entry | Catalyst | % ee[b] |
|---|---|---|
| 1 | Boc-Pmh-OMe (**12**) | 19 |
| 2 | Boc-Pmh-Aib-OMe (**13**) | 33 |
| 3 | Boc-Pmh-Aib-Phe-OMe (**14**) | 33 |
| 4 | Boc-Pmh-Aib-Phe-D-Phe-OMe (**15**) | 40 |
| 5 | Boc-Pmh-Aib-Cha-hPhe-D-Phe-OMe (**16**) | 47 |
| 6 | Boc-Pmh-Aib-Chg-Gln(Trt)-D-Phe-Phe-OMe (**11**) | 61 |
| 7 | Boc-Pmh-Aib-Chg-Gln(Trt)-D-Phe-(Boc)Trp-Phe-OMe (**17**) | 73 |
| 8 |  (**18**) | 78 |
| 9 | Boc-Pmh-Aib-Chg-Gln(Trt)-D-Phe-D-Pip-Cha-Phe-Phe-OMe (**19**) | 75 |
| 10 | Boc-Pmh-Aib-Chg-Gln(Trt)-D-Phe-D-Pip-Cha-Val-(Boc)Trp-Phe-OMe (**20**) | 74 |

[a] All reactions were conducted at 25 °C and proceeded to >75% conversion within 16 h as determined by $^1$H NMR.
[b] Determined by chiral HPLC. Reported ee values are the average of at least two runs.

to determine whether alteration of other reaction parameters could lead to improved selectivity and overall efficiency.[25] We also set out to determine whether the optimized reaction conditions were specific for 2-nitrobenzaldehyde. A variety of aromatic aldehydes were found to provide acceptable levels of reactivity in the MVK-based MBH reaction. As Table 2 illustrates, we observed 81% ee and 88% yield when 3-methoxy-2-nitrobenzaldehyde was used as a substrate (entry 5). Nitronaphthaldehyde participated in the MBH reaction affording **22** in up to 73% ee and in 92% yield (entry 2). *p*-Nitrobenzaldehyde and dinitrobenzaldehyde undergo the MBH reaction with MVK in 69 and 63% ee, respectively (81% yield, entry 3; 89% yield, entry 7). Another aldehyde examined was *o*-trifluoromethylbenzaldehyde, which afforded MBH product **23** in 71% ee and 52% yield (entry 4). Furaldehyde participates in the reaction generating MBH product **25** in 63% ee (entry 6).[26] In addition, 2-fluorobenzaldehyde undergoes the MBH reaction under the optimized reaction conditions in 65% ee with 55% yield (entry 9). Finally, two aldehydes which provided lower selectivities under the reaction conditions were 3-nitrobenzaldehyde and benzaldehyde, affording selectivities of 45 and 41% ee, respectively (entries 8 and 10).

**Table 2**. Substrate screen for the MVK-MBH reaction with co-catalyst **18**/Pro[a]

| Entry | Substrate | BH product | % Yield | % ee[b] |
|---|---|---|---|---|
| 1 |  |  **21** | 81 | 78 |
| 2 |  |  **22** | 92 | 73 |
| 3 |  |  **1** | 81 | 69 |
| 4 |  |  **23** | 52 | 71 |
| 5 |  |  **24** | 88 | 81 |
| 6[c] |  |  **25** | 95 | 63 |
| 7 |  |  **26** | 89 | 63 |
| 8 |  |  **27** | 74 | 45 |
| 9 |  |  **28** | 55 | 65 |
| 10 |  |  **29** | 55 | 41 |

[a] All reactions were conducted at 25 °C and proceeded to >75% conversion within 16 h as established by $^1$H NMR. Isolated yields are after silica gel chromatography.

[b] Enantioselectivities were determined by chiral HPLC. Reported ee values are the average of at least two runs.

[c] Reaction with furaldehyde, yield refers to conversion by $^1$H NMR; isolated yields after catalytic hydrogenation of the olefin are comparable.

Other aldehydes in addition to those listed in Table 2 were examined as possible substrates for this reaction. These included a variety of aliphatic, 'nonactivated' aromatic aldehydes, and unsaturated aldehydes. Unfortunately, no reaction was observed with the following aldehydes: propionaldehyde, isobutyraldehyde, *trans*-cinnamaldehyde, cyclohexanecarboxaldehyde, 1-naphthaldehyde, hydrocinnamaldehyde, and *o*-tolualdehyde. The scope of the ketone partner was also investigated. Under the optimized reaction conditions, ethyl vinyl ketone (EVK) participates in the reaction with 2-nitrobenzaldehyde to deliver the product with a reduced selectivity of 69% ee. Other substituted ketones we examined afforded no reaction under the optimized conditions. For example, phenyl vinyl ketone, cyclohexyl vinyl ketone, and *tert*-butyl vinyl ketone were all screened in this reaction and exhibited no reactivity. Furthermore, non-ketone-based α,β-unsaturated compounds such as various acrylates and acrylonitriles were also unreactive under the reaction conditions. Clearly, further studies of these systems are necessary if expansion of substrate scope and reaction generality is to be achieved.

To probe the nature of proline–peptide catalyst interaction, we set out to identify the importance of the proline component in these reactions. In the absence of proline, catalyst **18** affords <10% ee, with low conversion. As noted earlier, the NMI-proline co-catalyst system provided MBH product in <10% ee. Thus, we felt the specific interactions of the peptide–proline co-catalyst system could be important. To probe these effects, we performed parallel co-catalytic reactions with octapeptide **18** and both enantiomers of proline. Indeed, double stereodifferentiating effects were observed. Whereas the combination of L-proline and octapeptide **18** affords (*R*)-Morita–Baylis–Hillman product **21** in 78% ee, the catalyst pair of D-proline and octapeptide **18** yields (*S*)-**21** in a reduced 39% ee (Fig. 6). Intriguingly, the opposite enantiomer is formed when using D-proline in the reaction. The enantiodivergence occurring in this reaction is of interest because it suggests that the stereochemistry of proline dictates which enantiomer of MBH product is formed.[27,28]

In order to further investigate the role of the amino acid component, we screened a number of other amino acids and derivatives as the co-catalyst. As illustrated in Table 3, other amino acids such as valine, alanine, phenylalanine, histidine, and tyrosine (entry 1) do not afford appreciable levels of enantioselectivity in the reaction of 2-nitrobenzaldehyde and MVK with peptide **18**. Protected versions of the amino acids are also not selective (entry 2). Of interest is sarcosine (entry 4), in stark contrast to glycine (entry 3), indeed affords

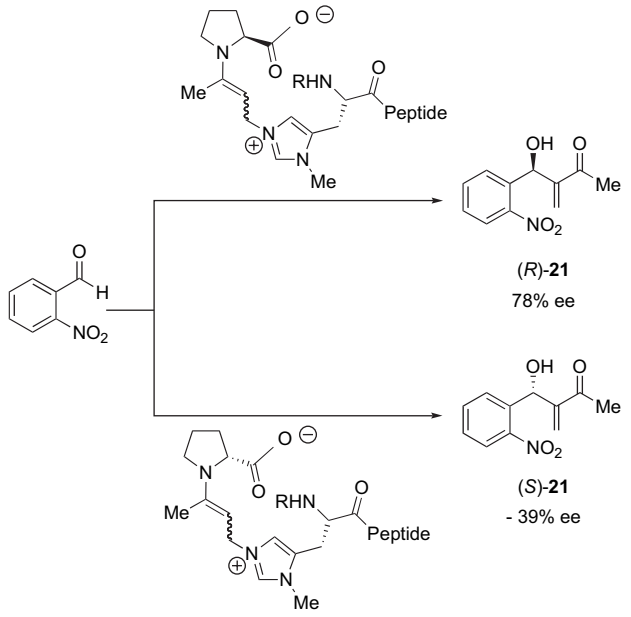
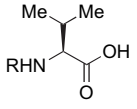
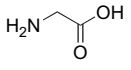
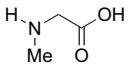
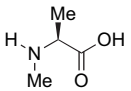
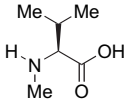
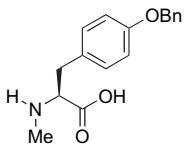



**Figure 6**. Matched and mismatched pairs of co-catalysts with proline and peptide **18**.

modest levels of enantioselectivity in the MBH reaction with peptide **18**. Because sarcosine provided appreciable levels of selectivity (44% ee in the MBH reaction with peptide **18**), we felt that screening a variety of *N*-methyl amino acids could provide useful information. Thus, a number of *N*-methyl amino acids were synthesized and screened; most of these amino acid derivatives afforded <11% ee for the MBH reaction (entries 6 and 7).[29] However, as shown in Table 3, *N*-methyl alanine (entry 5) afforded up to 31% ee in the reaction. From the data, one could conclude that more sterically hindered *N*-methyl amino acids begin to erode selectivity; however, sarcosine and *N*-methyl alanine allow for modest levels of enantiodiscrimination.

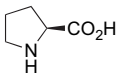
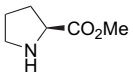
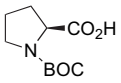
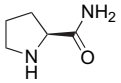
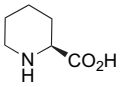
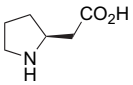
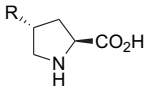
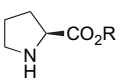
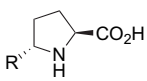
In addition to screening amino acid and amino acid derivatives as co-catalysts for the MBH reaction, we also examined other proline derivatives to explore the unique role of proline as a co-catalyst with peptide **18**. Simple modifications to the proline bifunctional nature (i.e., the amine and carboxylic acid termini, as in entries 2–4, 8, and 9; Table 4[30]) yield nonselective reactions with enantioselectivities of <10% ee. Furthermore, subtle alterations to the proline framework such as pipecolinic acid and homo-proline (entries 5 and 6)

**Table 3**. Amino acid co-catalysts in the MBH reaction with peptide **18**[a]

| Entry | Co-catalyst | % ee[b] |
|---|---|---|
| 1 | (L)-Val, (L)-Ala, (L)-Phe, (L)-His, (L)-Tyr, (D)-Phe | <10 |
| 2 |  R = BOC, FMOC | <10 |
| 3 |  | <10 |
| 4 |  | 44 |
| 5 |  | 31 |
| 6 |  | 11 |
| 7 |  | <10 |

[a] All reactions were conducted at 25 °C.
[b] Determined by chiral HPLC. Reported ee values are the average of at least two runs.

**Table 4**. Proline derivatives as catalysts in the MBH reaction with **18**[a]

| Entry | Compound | % ee[b] |
|---|---|---|
| 1 |  | 78 |
| 2 |  | <10 |
| 3 |  | <10 |
| 4 |  | <10 |
| 5 |  | 21 |
| 6 |  | 35 |
| 7 |  R = O*t*Bu<br>R = OH | 39<br><10 |
| 8 |  | <10 |
| 9 |  R = Li or Na | <10 |
| 10 |  R = Me, Ph, vinyl | 33–40 |

[a] All reactions were conducted at 25 °C.
[b] Determined by chiral HPLC. Reported ee values are the average of at least two runs.

afforded significantly reduced selectivities (21 and 35% ee, respectively). The reduced selectivity of pipecolinic acid is particularly noteworthy in light of our recent observation that NMI-pipecolinic acid is a particularly effective co-catalyst system for the intramolecular version of the MBH reaction.[5a] Hydroxy-proline derivatives also yield reduced selectivities (entry 7, 39 and <10% ee, depending on the protection of the hydroxyl group). In addition, 5-substituted proline derivatives were also synthesized and examined. 5-Substituted methyl, phenyl, and vinyl prolinates[31] (entry 10) were tested as co-catalysts in the MBH reaction with peptide **18**. These derivatives also provided lower selectivity than proline (entry 1) affording 33–40% ee in the MBH reaction.[32]

## 3. Conclusions

The data collected thus far indicate that a specific peptide–proline co-catalyst interaction may operate to afford an enantioselective reaction. A cohesive transition state assembly such as **30** could be operative (Fig. 7a). Enamines derived from proline have been shown to be effective asymmetric scaffolds for enantioselective reactions.[33] Perhaps the Pmh nucleophilic amine of the peptide catalyst adds to the proline iminium ion formed between MVK and proline. The addition product **30** could be stabilized by hydrogen bonding of the peptide backbone with the carboxylic acid of proline. However, the possibility of a two-catalyst transition state involving the peptide and proline-MVK conjugate addition product **31** is also a possible transition state (Fig. 7b). Not surprisingly, control experiments involving MVK and proline alone show efficient conjugate addition of the amine to the enone.

Exactly, which intermediates and transition states operate, **30** or **31**, a combination of both, or even another alternative transition state, is a matter of current investigation in our laboratory.[34] The possibility to fine-tune these peptide–proline interactions also presents a possible strategy for asymmetric catalyst development. Uncovering the identity of the non-covalent interactions responsible for the high levels of enantioselectivity observed for this reaction remains a challenge. In addition, understanding the precise role of the helix-inducing residue Aib, which proved to be important in obtaining selective peptide catalysts, represents another important task in our ongoing studies.[13]

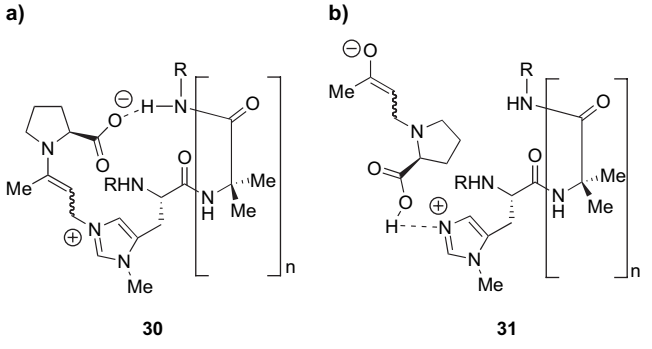



**Figure 7**. Possible transition state assemblies involving (a) proline–enamine intermediates and (b) peptide–proline-MVK conjugate addition product intermediates.

In summary, we have demonstrated success in the catalytic, asymmetric ketone-based Morita–Baylis–Hillman reaction using methyl vinyl ketone and a variety of aromatic aldehydes. Our catalyst system involves a peptide-based catalyst in the presence of proline as a co-catalyst. This co-catalyst system has enabled state-of-the-art enantioselectivities in the intermolecular MVK-MBH reaction with aldehydes, affording enantioselectivities in up to 81% ee. We have uncovered a unique peptide–proline co-catalyst interaction. Understanding such interactions could enable the discovery of other selective peptide catalysts and co-catalyst interactions, which could serve as catalysts for other carbon–carbon bond-forming reactions and group transfers. These explorations are currently underway in our laboratory.

## 4. Experimental

### 4.1. General

**4.1.1. General procedures.** Proton NMR spectra were recorded on a Varian 400 spectrometer. Proton chemical shifts are reported in parts per million ($\delta$) relative to internal tetramethylsilane (TMS, $\delta$, 0.0 ppm), or with the solvent reference relative to TMS employed as an internal standard ($CDCl_3$, $\delta$, 7.26 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m)], coupling constants [hertz], integration). Carbon NMR spectra were recorded on a Varian 400 (100 MHz) or 500 (125 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in parts per million ($\delta$) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, $\delta$, 77.0 ppm). All NMR spectra were acquired at ambient temperature. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 Å $F_{254}$ precoated plates (0.25 mm thickness). TLC $R_f$ values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$, cerium ammonium molybdenate (CAM), or ninhydrin solutions. Flash column chromatography was performed using silica gel 60 Å (32–63 μm). Optical rotations were recorded on a Rudolph Research Analytical Autopol IV Automatic polarimeter at the sodium D line (path length 50 mm). High resolution mass spectra were acquired in the Mass Spectrometry facility at Boston College (Chestnut Hill, MA) or at the University of Illinois (Urbana-Champaign, IL). The method of ionization is indicated in parenthesis.

Analytical and preparative reverse phase HPLC were performed on a Rainin SD-200 chromatograph equipped with a single wavelength UV detector (214 or 254 nm). Analytical normal phase HPLC was performed on a Hewlett–Packard 1100 Series chromatograph equipped with a diode array detector (214 and 254 nm). All reactions were carried out under a nitrogen atmosphere employing oven- and flame-dried glassware. All solvents were distilled from appropriate drying agents prior to use. Benzaldehyde and 2-furaldehyde were freshly distilled while all other aldehydes were used as received. Methyl vinyl ketone was used as received (Aldrich

Chemical Company, 99%). HPLC grade chloroform was purified by the method of Perrin.[35] $CDCl_3$ was purchased from Cambridge Isotope Laboratories, Inc., and used as received in the catalytic reactions.[36] Stereochemical proofs were conducted as previously reported.[37]

**4.1.2. Peptide synthesis.** Peptides **11–20** were synthesized on commercially available Fmoc-Phe-Wang polystyrene solid support. Couplings were performed with 4 equiv of amino acid, 4 equiv of HBTU, and 8 equiv Hünig's base in DMF, for 3 h. Deprotections were performed in the presence of 20% piperidine in DMF for 20 min (to minimize diketopiperazine formation; dipeptides were deprotected with 50% piperidine in DMF for 5 min). Peptides were cleaved from solid support by using a mixture of MeOH/DMF/$Et_3N$ (9:1:1) for 3 days. The peptides were characterized by electrospray mass spectrometry ($ESI^+$) and used in reaction screens without further purification.

**4.1.3. Data for peptides 11–20.**

**4.1.3.1. Boc-Pmh-OMe (12).** $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.39 (s, 1H), 6.78 (s, 1H), 5.22 (br d, $J$=7.6 Hz, 1H), 4.54 (m, 1H), 3.75 (s, 3H), 3.58 (s, 3H), 3.09 (m, 2H), 1.43 (s, 9H); TLC $R_f$ 0.51 (8% MeOH/$CH_2Cl_2$); exact mass calcd for $[C_{13}H_{21}N_3O_4+H]^+$ requires $m/z$ 284.1610. Found 284.1609 ($FAB^+$). HPLC retention time 1.4 min on a RP-18 X Terra (Waters) column eluting with 75% MeOH/water at a flow rate of 0.3 mL/min.

**4.1.3.2. Boc-Pmh-Aib-OMe (13).** $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.40 (s, 1H), 6.87 (s, 1H), 6.61 (s, 1H), 5.17 (s, 1H), 4.27 (m, 1H), 3.73 (s, 3H), 3.62 (s, 3H), 3.03 (d, $J$=6.4 Hz, 2H), 1.50 (s, 3H), 1.49 (s, 3H), 1.44 (s, 9H); TLC $R_f$ 0.40 (8% MeOH/$CH_2Cl_2$); exact mass calcd for $[C_{17}H_{28}N_4O_5+H]^+$ requires $m/z$ 369.2138. Found 369.2138 ($FAB^+$). HPLC retention time 1.4 min on a RP-18 X Terra (Waters) column eluting with 75% MeOH/water at a flow rate of 0.3 mL/min.

**4.1.3.3. Boc-Pmh-Aib-Phe-OMe (14).** $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.39 (s, 1H), 7.30–7.11 (m, 5H), 6.81 (s, 1H), 6.78 (d, $J$=7.6 Hz, 1H), 6.73 (s, 1H), 5.25 (d, $J$=6.4 Hz, 1H), 4.82 (dd, $J$=13.6 Hz, 6.4 Hz, 1H), 4.19 (m, 1H), 3.72 (s, 3H), 3.59 (s, 3H), 3.06 (m, 4H), 1.45 (s, 3H), 1.44 (s, 3H), 1.43 (s, 9H); TLC $R_f$ 0.43 (8% MeOH/$CH_2Cl_2$); exact mass calcd for $[C_{26}H_{37}N_5O_6+H]^+$ requires $m/z$ 516.2822. Found 516.2823 ($FAB^+$). HPLC retention time 2.0 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

**4.1.3.4. Boc-Pmh-Aib-Phe-D-Phe-OMe (15).** $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.43 (s, 1H), 7.33–7.15 (m, 10H), 6.86 (s, 1H), 6.76 (d, $J$=7.6 Hz, 1H), 6.58 (s, 1H), 5.10 (d, $J$=6.0 Hz, 1H), 4.80–4.69 (m, 2H), 4.25–4.20 (m, 1H), 3.65 (s, 3H), 3.60 (s, 3H), 3.39 (m, 2H), 3.16–3.04 (m, 3H), 2.98–2.88 (m, 2H), 1.44–1.40 (m, 15H); TLC $R_f$ 0.44 (8% MeOH/$CH_2Cl_2$); exact mass calcd for $[C_{35}H_{46}N_6O_7+Na]^+$ requires $m/z$ 685.3326. Found 685.3322 ($ESI^+$). HPLC retention time 2.5 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

**4.1.3.5. Boc-Pmh-Aib-Cha-hPhe-D-Phe-OMe (16).** $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (d, $J$=8.8 Hz, 1H), 7.37 (s, 1H), 7.30–7.13 (m, 7H), 6.87 (s, 1H), 6.79 (s, 1H), 5.45 (d, $J$=5.3 Hz, 1H), 4.64 (m, 1H), 4.41 (m, 1H), 4.33 (m, 1H), 4.01 (m, 1H), 3.61 (s, 3H), 3.27 (s, 3H), 3.17–3.07 (m, 2H), 3.05 (d, $J$=4.4 Hz, 1H), 3.01 (d, $J$=4.0 Hz, 1H), 2.81 (dd, $J$=16.0 Hz, 9.6 Hz, 2H), 2.68 (m, 2H), 2.40–2.30 (m, 2H), 2.13–1.90 (m, 4H), 1.80–1.64 (m, 8H), 1.54 (s, 3H), 1.49 (s, 3H), 1.46 (s, 9H), 1.25–0.94 (m, 4H); TLC $R_f$ 0.53 (10% MeOH/$CH_2Cl_2$); exact mass calcd for $[C_{45}H_{63}N_7O_8+H]^+$ requires $m/z$ 830.4816. Found 830.4817 ($FAB^+$). HPLC retention time 2.6 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

**4.1.3.6. Boc-Pmh-Aib-Chg-(trt)Gln-D-Phe-Phe-OMe (11).** $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.52 (d, $J$=8.0 Hz, 2H), 7.31–7.07 (m, 27H), 7.03–6.91 (m, 2H), 6.84 (s, 1H), 5.47 (s, 1H), 4.74–4.67 (m, 1H), 4.51–4.45 (m, 1H), 4.41–4.25 (m, 1H), 4.20–4.16 (m, 1H), 4.07–4.05 (m, 1H), 3.50 (s, 3H), 3.26–3.21 (m, 1H), 3.18 (s, 3H), 2.99–2.94 (m, 2H), 2.72–2.66 (m, 2H), 2.36–2.06 (m, 5H), 1.80–1.09 (m, 27H); TLC $R_f$ 0.43 (8% MeOH/$CH_2Cl_2$); exact mass calcd for $[C_{67}H_{81}N_9O_{10}+Na]^+$ requires $m/z$ 1194.6004. Found 1194.6016 ($ESI^+$). HPLC retention time 9.7 min on a RP-18 X Terra (Waters) column eluting with 75% MeOH/water at a flow rate of 0.2 mL/min.

**4.1.3.7. Boc-Pmh-Aib-Chg-(trt)Gln-D-Phe-(Boc)Trp-Phe-OMe (17).** $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.07 (br d, $J$=7.8 Hz, 1H), 7.58–7.48 (m, 4H), 7.27–7.11 (m, 30H), 7.00 (s, 1H), 6.83 (s, 1H), 6.69 (br d, $J$=8.0 Hz, 1H) 5.54 (s, 1H), 4.67–4.55 (m, 2H), 4.10–3.97 (m, 3H), 3.42 (s, 3H), 3.30–3.20 (m, 2H), 3.18 (s, 3H), 3.13–2.97 (m, 2H), 2.92–2.86 (m, 3H), 2.76–2.70 (m, 2H), 2.39–2.29 (m, 3H), 2.18–2.10 (m, 5H), 1.85–1.50 (m, 14H), 1.49–1.36 (m, 6H), 1.30–1.00 (m, 12H); TLC $R_f$ 0.48 (8% MeOH/$CH_2Cl_2$); exact mass calcd for $[C_{83}H_{99}N_{11}O_{13}+H]^+$ requires $m/z$ 1458.7502. Found 1458.7506 ($FAB^+$). HPLC retention time 5.1 min on a RP-18 X Terra (Waters) column eluting with 90% MeOH/water at a flow rate of 0.2 mL/min.

**4.1.3.8. Boc-Pmh-Aib-Chg-(trt)Gln-D-Phe-D-Pip-Cha-Phe-OMe (18).** $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.40 (d, $J$=7.6 Hz, 1H), 7.86 (d, $J$=8.4 Hz, 1H), 7.60 (d, $J$=4.0 Hz, 1H), 7.38–7.06 (m, 24H), 6.90, (s, 1H), 6.78–6.77 (m, 2H), 5.99, (d, $J$=4.8 Hz, 1H), 4.60–4.52 (m, 2H), 4.35–4.32 (m, 2H), 4.15–4.10 (m, 3H), 3.54 (s, 3H), 3.27–3.12 (m, 3H), 2.97–2.94 (m, 4H), 2.85–2.78 (m, 2H), 2.62–2.57 (m, 2H), 2.48–2.41 (m, 2H), 2.25–2.19 (m, 5H), 2.11–2.04 (m, 2H), 1.75–1.12 (m, 44H); TLC $R_f$ 0.47 (8% MeOH/$CH_2Cl_2$); exact mass calcd for $[C_{82}H_{105}N_{11}O_{12}+H]^+$ requires $m/z$ 1436.8022. Found 1436.8035 ($ESI^+$). HPLC retention time 3.4 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

**4.1.3.9. Boc-Pmh-Aib-Chg-(trt)Gln-D-Phe-D-Pip-Cha-L-Phe-Phe-OMe (19).** $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.31 (br s, 1H), 7.85 (br s, 1H), 7.59 (br s, 1H), 7.47 (br s, 1H), 7.26–7.08 (m, 27H), 6.99 (br s, 1H), 6.86 (m, 2H), 6.76 (s, 1H), 6.41 (s, 1H), 5.88 (s, 1H), 4.62–4.54 (m, 2H), 4.36–4.26 (m, 4H), 4.13 (m, 2H), 3.59 (s, 3H), 3.17 (s, 3H), 2.98–2.90 (m, 2H), 2.84–2.79 (m, 2H), 2.62–2.54 (m, 2H), 2.48–2.40 (m, 2H), 2.25–2.20 (m, 2H), 2.09–2.03 (m, 2H),

1.74–0.87 (m, 51H); TLC $R_f$ 0.40 (8% MeOH/$CH_2Cl_2$); exact mass calcd for $[C_{91}H_{114}N_{12}O_{13}+H]^+$ requires *m/z* 1583.8706. Found 1583.8703 ($ESI^+$). HPLC retention time 6.2 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

**4.1.3.10. Boc-Pmh-Aib-Chg-(trt)Gln-D-Phe-D-Pip-Cha-Val-(Boc)Trp-Phe-OMe (20).** $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 8.74 (br s, 1H), 8.17 (br s, 1H), 7.87 (d, *J*=7.2 Hz, 1H), 7.64 (s, 1H), 7.62 (s, 1H), 7.40–6.91 (m, 30H), 6.75 (s, 2H), 6.71–6.89 (m, 1H), 5.98 (s, 1H), 4.74–4.70 (m, 5H), 4.48–4.08 (m, 6H), 3.64 (s, 3H), 3.23–2.84 (m, 15H), 2.25–2.09 (m, 4H), 1.69–0.76 (60H); TLC $R_f$ 0.33 (8% MeOH/$CH_2Cl_2$); exact mass calcd for $[C_{103}H_{132}N_{14}O_{16}+Na]^+$ requires *m/z* 1843.9843. Found 1843.9840 ($ESI^+$). HPLC retention time 45.4 min on a RP-18 X Terra (Waters) column eluting with 55% MeOH/water at a flow rate of 0.2 mL/min.

### 4.1.4. General procedure for the Morita–Baylis–Hillman reaction.

**4.1.4.1. Enantioselective Morita–Baylis–Hillman reaction employing catalyst 18 with product isolation.** To a 10 mL round bottom flask, flame-dried and equipped with a stir bar, were added peptide **18** (0.0015 mmol), dissolved in $CHCl_3$/THF (1:2, 0.5 M), L-proline (0.0015 mmol), 2-nitrobenzaldehyde (0.015 mmol), and methyl vinyl ketone (0.029 mmol). The resulting mixture was stirred until complete loss of starting material was observed by TLC (2:1 hexane/ethyl acetate). The reaction mixture was diluted with chloroform and purification via silica gel chromatography ($SiO_2$, $CHCl_3$) afforded 2.7 mg (81%) of **21** as a pale yellow oil.

Compound **21**: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.98 (d, *J*=8.4 Hz, 1H), 7.78 (d, *J*=7.7 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.47 (t, *J*=7.2 Hz, 1H), 6.22 (s, 1H), 6.17 (s, 1H), 5.79 (s, 1H), 3.49 (br s, 1H), 2.37 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 199.5, 149.0, 147.8, 136.7, 133.5, 128.8, 128.5, 126.6, 124.5, 67.1, 26.2; IR (film, $cm^{-1}$) 3414, 1675, 1525, 1351; TLC $R_f$ 0.52 (40% ethyl acetate/hexane); $[\alpha]_D$ −114 (*c* 1.0, $CHCl_3$); exact mass calcd for $[C_{11}H_{11}NO_4+Na]^+$ requires *m/z* 244.0586. Found 244.0585 ($ESI^+$). Assay of enantiomeric purity: Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/2-proponal 95:5; flow rate 0.75 mL/min; 29.8 min (minor ent), 32.5 min (major ent).

Compound **22**: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.99 (d, *J*=8.8 Hz, 1H), 7.91 (d, *J*=7.3 Hz, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 7.66–7.58 (m, 3H), 6.29 (s, 1H), 6.00 (s, 1H), 5.89 (d, *J*=4.4 Hz, 1H), 3.51 (d, *J*=4.7 Hz, 1H), 2.36 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 199.3, 147.5, 146.2, 132.9, 130.8, 130.6, 128.5, 127.8, 127.7, 127.3, 124.0, 123.9, 121.5, 67.9, 26.2; IR (film, $cm^{-1}$) 3414, 2363, 2332, 1675, 1527, 1361; TLC $R_f$ 0.45 (40% ethyl acetate/hexane); $[\alpha]_D$ −196 (*c* 1.0, $CHCl_3$); exact mass calcd for $[C_{15}H_{13}N_1O_4+Na]^+$ requires *m/z* 294.0742. Found 294.0741 ($ESI^+$). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/2-propanol 93:7; flow rate 0.75 mL/min; 34.1 min (minor ent), 38.1 min (major ent).

Characterization of (*R*)-**1** has been previously reported.[8d]

**4.1.4.2. Proof of absolute stereochemistry.** The absolute stereochemistry of the major adduct **1** was determined by comparing the sign of the specific rotation with reported literature data. The kinetic resolution of the racemic compound **1** by Sharpless epoxidation using L-(+)-diethyl tartrate leads to preferentially recovered starting material of the (*S*)-configuration. Measurement of the optical rotation and comparison to the literature showed the sample to be of the (*R*)-configuration: $[\alpha]_D$ −3.8 (*c* 0.53, $CHCl_3$); literature for (*R*)-**1**: $[\alpha]_D$ −12.1 (*c* 0.53, $CHCl_3$).

Compound **23**: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.72 (d, *J*=7.7 Hz, 1H), 7.66 (d, *J*=7.7 Hz, 1H), 7.59 (m, 1H), 7.42 (t, *J*=7.7 Hz, 1H), 6.19 (s, 1H), 6.06 (br s, 1H), 5.54 (s, 1H), 3.42 (d, *J*=3.7 Hz, 1H), 2.39 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 199.9, 149.7, 139.2, 131.9, 127.7, 127.6, 127.3, 125.7, 122.6, 119.9, 67.3, 26.4; IR (film, $cm^{-1}$) 3420, 1678, 1312, 771; TLC $R_f$ 0.48 (30% ethyl acetate/hexane); $[\alpha]_D$ −31 (*c* 0.83, $CHCl_3$); exact mass calcd for $[C_{12}H_{11}O_2F_3+Na]^+$ requires *m/z* 267.0609. Found 267.0605 ($ESI^+$). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/2-proponal 95:5; flow rate 0.75 mL/min; 13.2 min (minor ent), 15.5 min (major ent).

Compound **24**: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.43 (t, *J*=8.1 Hz, 1H), 7.14 (d, *J*=7.7 Hz, 1H), 6.99 (d, *J*=8.4 Hz, 1H), 6.24 (s, 1H), 5.96 (s, 1H), 5.66 (d, *J*=5.5 Hz, 1H), 3.89 (s, 3H), 3.46 (d, *J*=5.5 Hz, 1H), 2.34 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 199.7, 150.9, 147.8, 140.2, 134.7, 131.4, 128.1, 119.6, 112.4, 68.1, 56.8, 26.5; IR (film, $cm^{-1}$) 3414, 1674, 1531; TLC $R_f$ 0.30 (30% ethyl acetate/hexane); $[\alpha]_D$ −112 (*c* 1.0, $CHCl_3$); exact mass calcd for $[C_{12}H_{10}N_4O_4+Na]^+$ requires *m/z* 274.0691. Found 274.0699 ($ESI^+$). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/2-proponal 90:10; flow rate 0.75 mL/min; 30.7 min (minor ent), 33.7 min (major ent).

Compound **25**: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.36 (s, 1H), 6.34–6.32 (m, 1H), 6.25–6.24 (m, 2H), 6.1 (s, 1H), 5.63 (d, *J*=5.8 Hz, 1H), 3.26 (br s, 1H), 2.38 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 199.2, 154.2, 147.2, 141.6, 126.4, 109.9, 106.6, 65.2, 25.7; IR (film, $cm^{-1}$) 3320, 2957, 2923, 2852, 1714, 1667, 1510, 1462, 1376; TLC $R_f$ 0.56 (30% ethyl acetate/hexane); $[\alpha]_D$ −6.5 (*c* 0.31, $CHCl_3$); exact mass calcd for $[C_9H_{10}O_3+Na]^+$ requires *m/z* 189.0528. Found 189.0526 ($ESI^+$). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/ethanol 95:5; flow rate 0.75 mL/min; 29.0 min (major ent), 37.0 min (minor ent).

Compound **26**: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 8.80 (d, *J*=2.2 Hz, 1H), 8.48 (dd, *J*=8.4, 2.2 Hz, 1H), 8.05 (d, *J*=8.8 Hz, 1H), 6.30 (s, 1H), 6.23 (s, 1H), 5.85 (s, 1H), 3.55 (br s, 1H), 2.38 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 199.5, 148.1, 147.9, 147.2, 143.2, 130.6, 127.3, 127.1, 120.1, 67.4, 25.9; IR (film, $cm^{-1}$) 3408, 3106,

2357, 1673, 1606, 1536, 1347; TLC $R_f$ 0.43 (40% ethyl acetate/hexane); $[\alpha]_D$ −135 (*c* 1.0, $CHCl_3$); exact mass calcd for $[C_{11}H_{10}N_2O_6+Na]^+$ requires *m/z* 289.0437. Found 289.0430 ($ESI^+$). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel OJ column (Diacel). Conditions: hexane/ethanol 90:10; flow rate 0.75 mL/min; 54.3 min (major ent), 63.1 min (minor ent).

Compound **27**: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 8.22 (s, 1H), 8.13 (m, 1H), 7.74 (d, *J*=7.7 Hz, 1H), 7.52 (t, *J*=7.7 Hz, 1H), 6.29 (s, 1H), 6.09 (s, 1H), 5.67 (s, 1H), 3.36 (br s, 1H), 2.37 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 200.1, 149.1, 148.4, 144.1, 132.9, 129.5, 127.9, 122.8, 121.6, 72.4, 26.8; IR (film, $cm^{-1}$) 3439, 1671, 1529, 1349; TLC $R_f$ 0.44 (30% ethyl acetate/hexane); $[\alpha]_D$ −14 (*c* 1.0, $CHCl_3$); exact mass calcd for $[C_{11}H_{11}NO_4+Na]^+$ requires *m/z* 244.0586. Found 244.0589 ($ESI^+$). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/ethanol 90:10; flow rate 0.75 mL/min; 19.9 min (minor ent), 35.3 min (major ent).

Compound **28**: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.50 (m, 1H), 7.28 (m, 1H), 7.17 (m, 1H), 7.03 (m, 1H), 6.19 (s, 1H), 5.89 (br d, 1H), 5.87 (s, 1H), 3.44 (br d, *J*=5.1 Hz, 1H), 2.38 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 200.0, 160.6, 158.2, 148.4, 128.8, 127.7, 126.5, 123.7, 114.9, 65.9, 26.1; IR (film, $cm^{-1}$) 3416, 1675, 1490; TLC $R_f$ 0.48 (30% ethyl acetate/hexane); $[\alpha]_D$ +20 (*c* 0.68, $CHCl_3$); exact mass calcd for $[C_{11}H_{11}O_2F+Na]^+$ requires *m/z* 217.0641. Found 217.0643 ($ESI^+$). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/ethanol 98:2; flow rate 0.75 mL/min; 34.2 min (minor ent), 39.8 min (major ent).

Compound **29**: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.33–7.22 (m, 5H), 7.78 (d, *J*=7.7 Hz, 1H), 6.15 (s, 1H), 5.98 (s, 1H), 5.56 (s, 1H), 3.55 (br s, 1H), 2.28 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 200.0, 149.9, 141.5, 128.1, 127.4, 126.4, 126.2, 72.2, 26.2; IR (film, $cm^{-1}$) 3414, 1673, 1369; TLC $R_f$ 0.47 (30% ethyl acetate/hexane); $[\alpha]_D$ −19 (*c* 0.23, $CHCl_3$); exact mass calcd for $[C_{11}H_{12}O_2+Na]^+$ requires *m/z* 199.0735. Found 199.0732 ($ESI^+$). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/ethanol 97:3; flow rate 0.75 mL/min; 31.1 min (minor ent), 35.7 min (major ent).

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23. We also synthesized peptides of shorter length, catalysts **12**–**15**, to determine if the length-selectivity trend would be apparent with smaller peptides. Shorter peptide lengths such as dipeptide **13**, tripeptide **14**, and tetrapeptide **15** did appear to follow this trend with the limited number of cases examined.
24. A brief study of the peptide/proline ratio revealed that 1:1 stoichiometry is optimal in the cases we explored.
25. In addition to solvent screens, temperature was also examined. A variety of ranges ($-20\ ^\circ C \rightarrow 50\ ^\circ C$) were screened, all of which afforded either low conversions to MBH product or significantly reduced enantioselectivities. Solvent screens with 21 different solvent combinations were examined. Mixtures (2:1) of either THF/$CHCl_3$ or toluene/$CHCl_3$ yielded similar selectivities of 78% ee in the MBH reaction of 2-nitrobenzaldehyde with peptide **18**.
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