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

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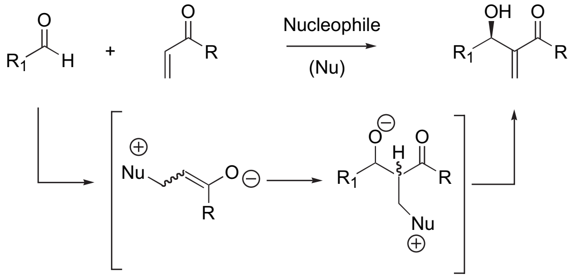
This article is dedicated to Professor David W. C. MacMillan on the occasion of his receiving the Tetrahedron Young Investigator Award

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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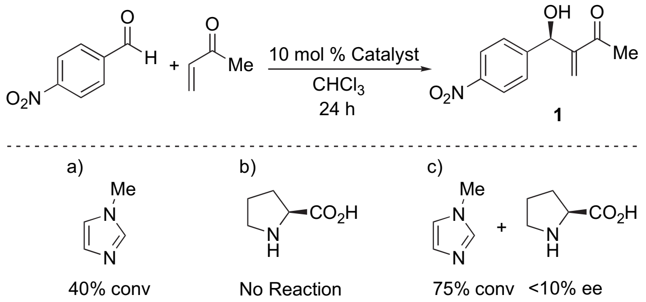

Figure 1. MBH reaction of 4-nitrobenzaldehyde and MVK in the presence of (a) NMI as catalyst, (b) Proline (Pro) as catalyst, and (c) co-catalyst combination of NMI and Pro.

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 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]

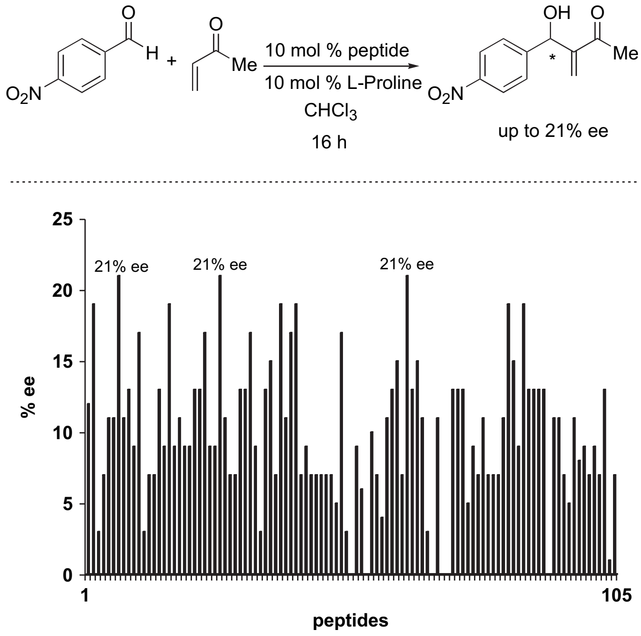

Figure 2. Initial screen of peptide catalysts in the MVK-MBH reaction.

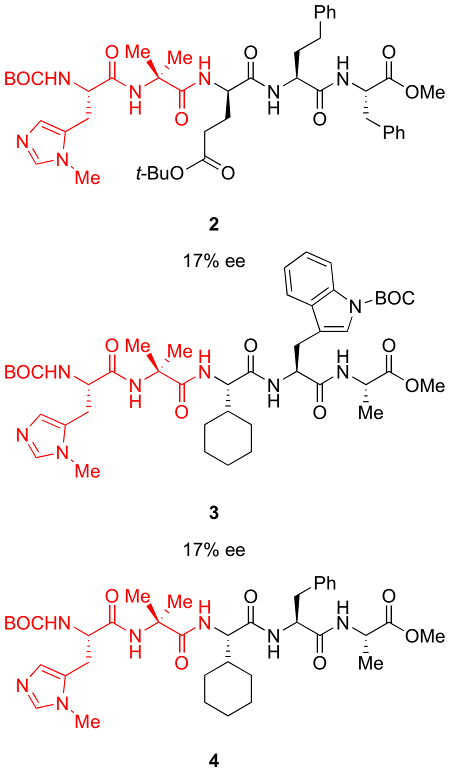

Figure 3. Selective pentapeptides which contain similar sequences.

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.