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α,*β*-Dehydroamino Acid Synthesis through Proline-Catalyzed Aldol Condensation with a Glycine Schiff Base

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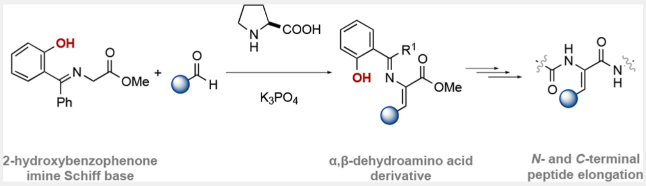
ABSTRACT: A general protocol for the synthesis of *α*,*β*-dehydroamino acids and their peptides was developed. Proline efficiently catalyzed an aldol condensation reaction of a glycine Schiff base with a variety of aldehydes. The hydroxy group on the benzophenone imine was crucial for high *Z*/*E* selectivity and further transimination for protecting group-free *α*,*β*-dehydroamino esters. Peptide elongation of both the C- and N-terminals highlighted the usefulness of our present protocol.



KEYWORDS: *α,β-dehydroamino acid, peptide, proline, aldol condensation, glycine Schiff base, transimination*

■ INTRODUCTION

α,*β*-Dehydroamino acids are useful for anchoring peptide conformations, as exemplified by the *β*-turn and 3_{10}-helix motifs with the acquisition of peptidase resistance.[1−3] Naturally occurring and biologically active peptides often contain *α*,*β*-dehydroamino acids (Scheme 1A).[4,5] *α*,*β*-Dehydroamino acids also serve as reactive amino acids, delivering a diverse set of peptides possessing unnatural *α*-amino acids.[6] Straightforward synthetic methods to elongate peptides in the same way as ordinary *α*-amino acids are highly desired.[7−11] Although synthetic approaches to peptides bearing *α*,*β*-dehydroamino acids have been intensively investigated, the results are quite limited due to the instability of *α*,*β*-dehydroamino acids. *α*,*β*-Dehydroamino acid-derived peptide synthesis is classically based on the elimination reaction of hydroxyl groups, such as serine and threonine, or olefination of prefunctionalized glycine derivatives.[12−18] These methods, however, are mainly limited to synthetic elongation at the C-terminal of *α*,*β*-dehydroamino acids, and synthetic elongation methods, especially at the N-terminal,[19−21] are largely unexplored (Scheme 1B).[22]

We envisioned that the amino acid Schiff base developed by O'Donnell and co-workers would be suitable for synthesizing *α*,*β*-dehydroamino acid, enabling elongation of both the N- and C-terminals in peptide synthesis.[23−37] The Schiff base derived from benzophenone is conventionally deprotected under acidic conditions, leading to undesired hydrolyzed *α*-keto ester products (Scheme 1B). We identified 2-hydroxybenzophenone imine as a viable protecting group[38−40] that could be removed by hydrogen-bonding activation under almost neutral conditions through transimination[41−47] due to its enhanced electrophilic nature, as exemplified by pyridoxal phosphate enzymes (Scheme 1C).[48−50] Various approaches to accessing *α*,*β*-dehydroamino acid using amino acid Schiff bases are reported, but these methods have not been applied to peptide synthesis.[51−54] Furthermore, previous reactions using glycine equivalents are burdened by tedious multistep sequences, the generation of a stoichiometric amount of waste, and a significantly limited substrate scope,[55−60] and no catalytic and environmentally benign process has yet been achieved.[61,62] Herein we described a general synthetic method for *α*,*β*-dehydroamino acid-derived peptides using an proline-catalyzed aldol condensation reaction (Scheme 1D). Elongation of both the C- and N-terminals was achieved using the 2-hydroxybenzophone imine Schiff base.

■ RESULTS AND DISCUSSION

The investigation was initiated using benzophenone imine-derived glycine Schiff base **1a** (Table 1, entry 1). Inexpensive L-proline was used as a catalyst. The combined use of a catalytic amount of proline and base promoted the reaction, delivering the product **3aa** in high yield. The *Z*/*E* ratio remained moderate, however, despite intensive optimization studies. Next, we turned our attention to 2-hydroxybenzophenone imine-derived glycine Schiff base **1b**.[38−40] The *Z*/*E* ratio improved dramatically, and the *Z*-configured product **3ba**, confirmed by single-crystal X-ray diffraction analysis, was obtained in high yield (entry 2).[63] Further base screening within a short period of the reaction time revealed that the *Z*/*E* ratio was lower in the initial stage of the reaction and converged to a thermodynamically stable *Z*-isomer over time

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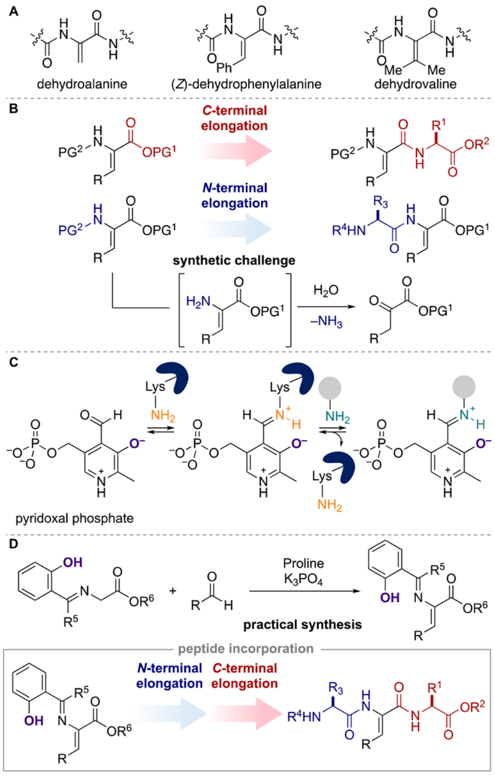
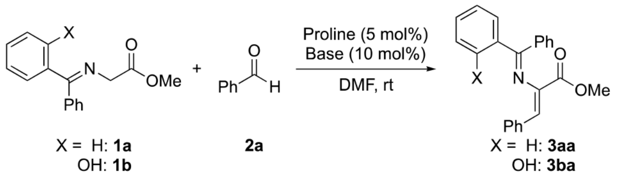
Scheme 1. α,β-Dehydroamino Acids and Peptides[a]



[a](A) Structures of α,β-dehydroamino acid and naturally occurring peptides. (B) Difficulties in elongating the α,β-dehydroamino acid at the N-terminal. (C) Pyridoxal phosphate enzyme- catalyzed transamination. (D) This work: General method to elongate both the C- and N-terminals.

Table 1. Optimization Study[a]



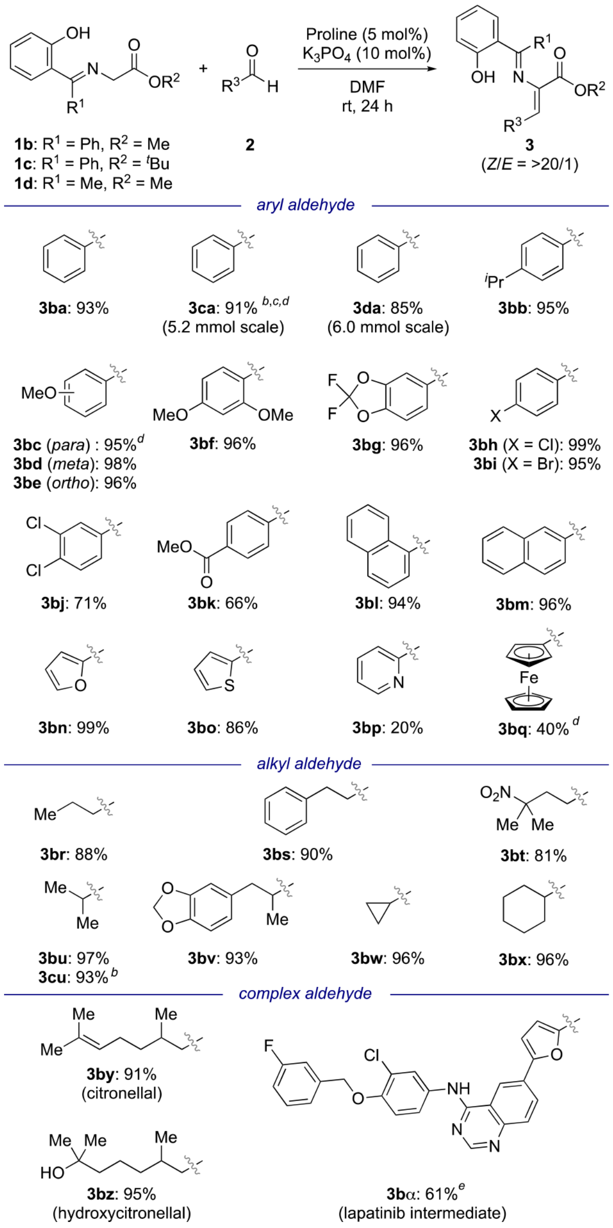
entry	X	base	time [h]	Z/E	3 yield [%]
1[b]	1a	K_3PO_4	24	2.3/1	97
2[b]	1b	K_3PO_4	24	>20/1	99
3	1b	Li_2CO_3	3		5
4	1b	Na_2CO_3	3	1.3/1	25
5	1b	K_2CO_3	3	3.0/1	60
6	1b	Cs_2CO_3	3	>20/1	51
7	1b	K_3PO_4	3	1.5/1	62
8	1b	K_2HPO_4	3	1.2/1	9
9	1b	K_3PO_4	24	>20/1	96
10	1b		24		N.D.
11[c]	1b	K_3PO_4	24		5
12[d]	1b	K_3PO_4	24		28
13[e]	1b	K_3PO_4	24		31

[a]Conditions: **1** (0.2 mmol), **2a** (0.24 mmol), 5 mol % proline, 10 mol % base, DMF (1.0 mL). ^1H NMR yields are shown. [b]10 mol % proline, 20 mol % K_3PO_4, 1.5 equiv of **2a**. 0.30 mmol scale. [c]Without proline. 2.0 equiv of **2a**. [d]50 mol % of pyrrolidine and acetic acid were used instead of proline. 1.0 equiv of K_3PO_4 was used. 0.30 mmol scale. [e]50 mol % of pyrrolidine and benzoic acid were used instead of proline. 1.0 equiv of mol % of K_3PO_4 was used.

($\Delta G^0 = 7.63$ kcal mol^{-1}).[64] (entries 3–9). The enhanced basic cesium carbonate reached a high Z/E ratio within 3 h, although the yield was only moderate (entry 6). Inexpensive tripotassium phosphate provided the product **3ba** in high yield with a high Z/E ratio by prolonging the reaction time (entry 9, optimal conditions). Both proline and base were crucial for promoting the reaction (entries 10,11). The importance of the combination of intramolecular pyrrolidine and carboxylic acid was confirmed by the intermolecular conditions (entries 12, 13).

With the optimized conditions in hand (Table 1, entry 9), we next explored the substrate scope (Scheme 2). The glycine *tert*-butyl ester-derived Schiff base **1c** was used and the product **3ca** was isolated in gram scale. The glycine Schiff base derived

Scheme 2. Substrate Scope[a]



[a]Conditions: **1** (0.2 mmol), **2** (0.24 mmol), DMF (1.0 mL). Isolated yields are shown. [b]15 mol % proline, 30 mol % of K_3PO_4. [c]25.5 h reaction time. [d]Isolated after treatment of $NaBH_4$ for the separation of aldehyde. [e]Z/E ratio was 6/1.

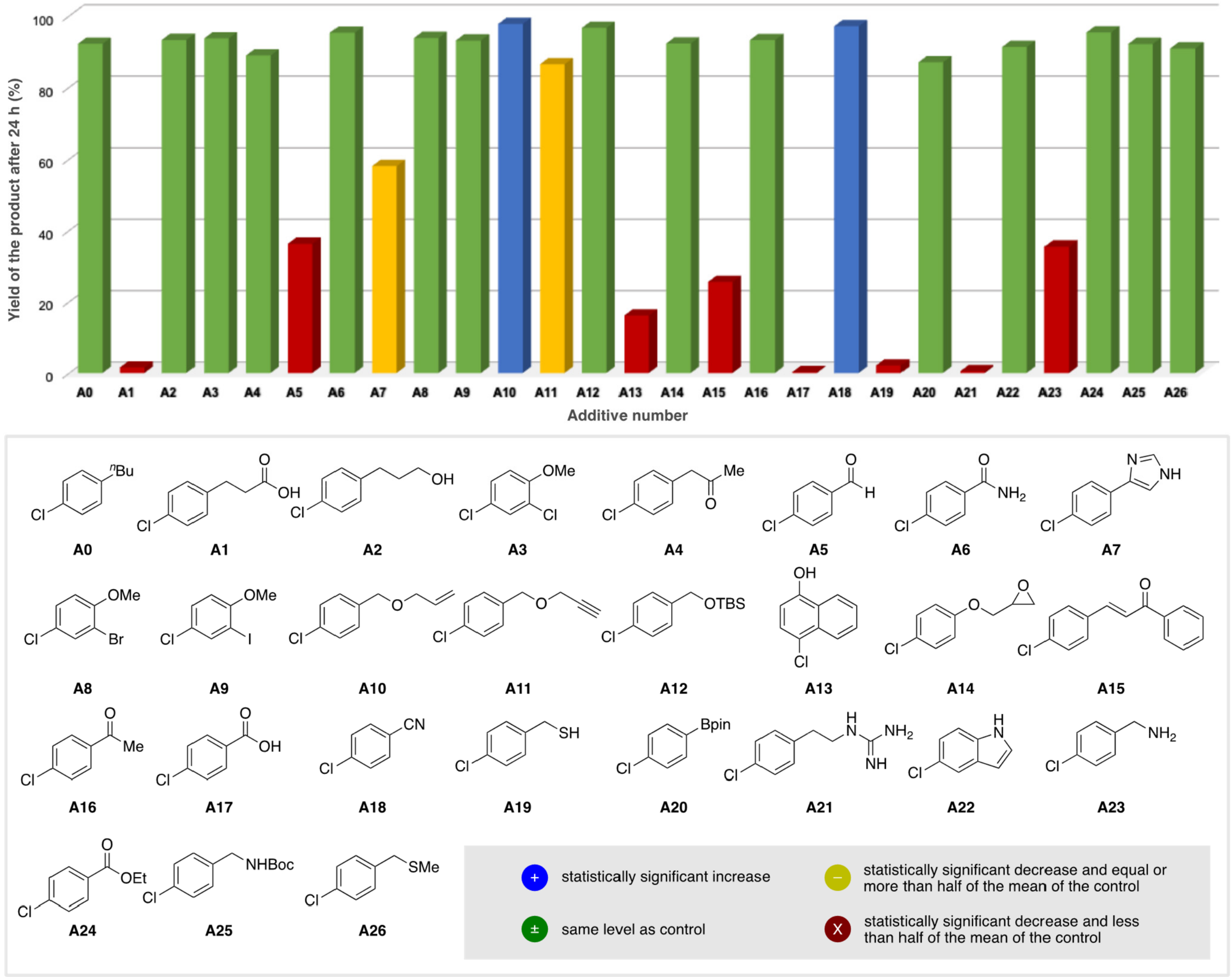


Figure 1. Summary of results using a functional group evaluation kit.

from 2-hydroxyacetophenone **1d**, which is easily removable, exhibited the same reactivity as **1c**. A wide range of substituents on the aryl group could be used without any detrimental effect (**3bb**−**3bi**). The electron-donating group at *para*, *meta*, and sterically hindered *ortho* positions was tolerated (**3bb**−**3be**). High yields were also observed when using disubstituted substrates (**3bf**, **3bg**). The halogen groups delivered α,β-dehydroamino acid derivatives in high yield (**3bh**, **3bi**). The present catalysis was less effective for dichloro-substituted and ester-substituted substrates (**3bj**, **3bk**). Naphthyl groups were applicable and the products were obtained in high yields (**3bl**, **3bm**). The furan and thiophene functionalities could be incorporated without any problem (**3bn**, **3bo**), while the pyridine and ferrocene functionalities provided the products with low yields (**3bp**, **3bq**).

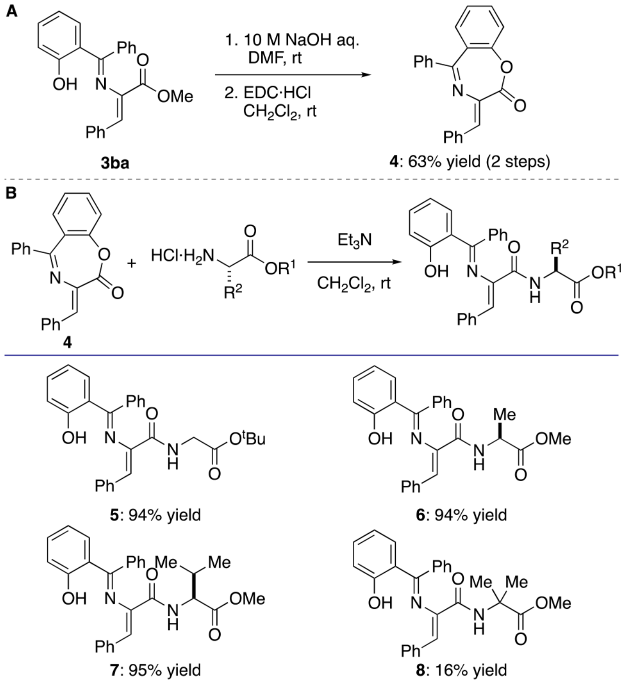
Our method was not confined to aryl aldehydes. Alkyl aldehydes, readily enolizable and prone to undergoing self-aldol reactions, were also suitable substrates for the synthesis of α,β-dehydroamino acid derivatives (**3br**−**3bx**). Several primary alkyl aldehydes afforded the products with the same efficiency as that of aryl aldehydes (**3br**−**3bt**). Various acyclic and cyclic alkyl aldehydes were also applicable to the present catalysis (**3bu**−**3bx**, **3cu**).

Several complex aldehydes were investigated next to demonstrate the utility of the present catalysis. Citronellal and protecting group-free hydroxycitronellal were used, affording the products in high yields (**3by**, **3bz**). A highly functionalized lapatinib intermediate was transformed into the corresponding α,β-dehydroamino acid derivatives in a synthetically useful yield, although a decreased Z/E ratio was observed (6/1) (**3b**$\boldsymbol{\alpha}$).

To confirm its further utility, the present catalytic method was evaluated using a functional group evaluation kit (Figure 1).[65−67] The yield of the product **3bu** was monitored for periods of 1 and 24 h in the presence of 1.0 equiv of compounds bearing various functional groups.[68] Wide functional group tolerances were confirmed using 26 additives, although significantly lower yields were observed using carboxylic acid (**A1**, **A17**), phenol **A13**, thiol **A19**, guanidine **A21**, and primary amine **A23** functionalities. These results indicated that acidic and highly basic or nucleophilic functionalities were not suitable for the present catalytic method. A decrease in the yields and consumption of the additives also occurred in the presence of aldehydes **A5** or α,β-unsaturated ketones **A15**, presumably due to the competitive addition reaction.

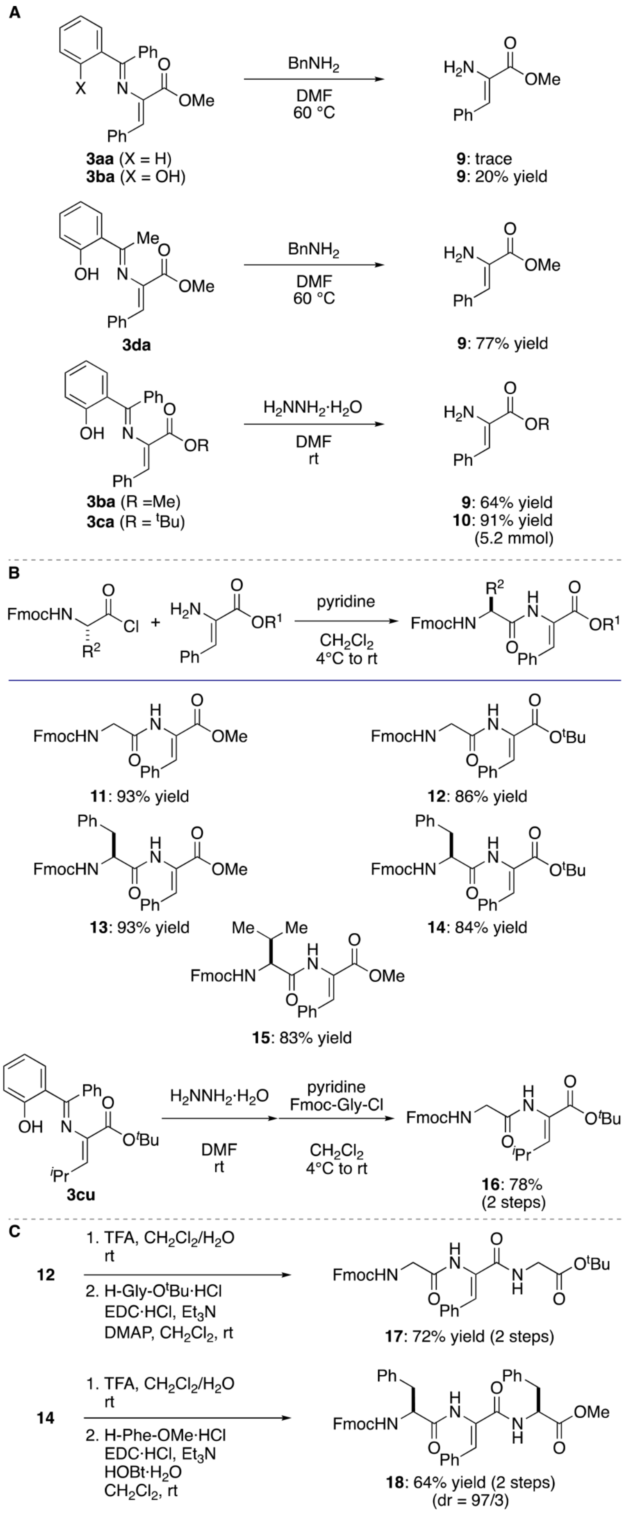
Our focus was directed toward the incorporation of α,β-dehydroamino acid derivatives synthesized into peptides in both the N- and C-directions. Hydrolysis of the methyl ester of **3ba** followed by condensation with a phenol group provided 7-membered product **4** (Scheme 3A). Further amidation of **4** with amino acid ester was achieved, providing the C-terminal elongated dipeptides **5**−**7** in high yields (Scheme 3B). Notably, a sterically hindered 2-aminoisobutyric acid (Aib) derivative could be incorporated to afford dipeptide **8**, although the chemical yield was not high.

Scheme 3. Deprotection of C-Terminal and Peptide Synthesis



Amino acid Schiff base is conventionally deprotected under mild acidic conditions. The α,β-dehydroamino acid Schiff base **3**, however, exclusively underwent hydrolysis under acidic conditions to afford undesired α-keto ester. Extensive screening revealed that deprotection of benzophenone-derived Schiff base **3aa** through transimination was difficult (Scheme 4A). In sharp contrast, transimination of 2-hydroxybenzophenone-derived Schiff base **3ba** with benzylamine proceeded to afford the product **9**. The 2-hydroxyacetophenone-derived Schiff base **3da** was a suitable substrate for transimination with benzylamine, providing the product **9** in high yield. Enhanced nucleophilic hydrazine provided product **9** in a synthetically useful yield. *tert*-Butyl ester **3ca** could be converted into the corresponding N-unprotected α,β-dehydroamino ester **10** in higher yield on a gram scale, presumably due to suppression of the hydrazide formation. These results demonstrated that the present method is a complementary approach for the synthesis of N-unprotected α,β-dehydroamino ester.[69−74]

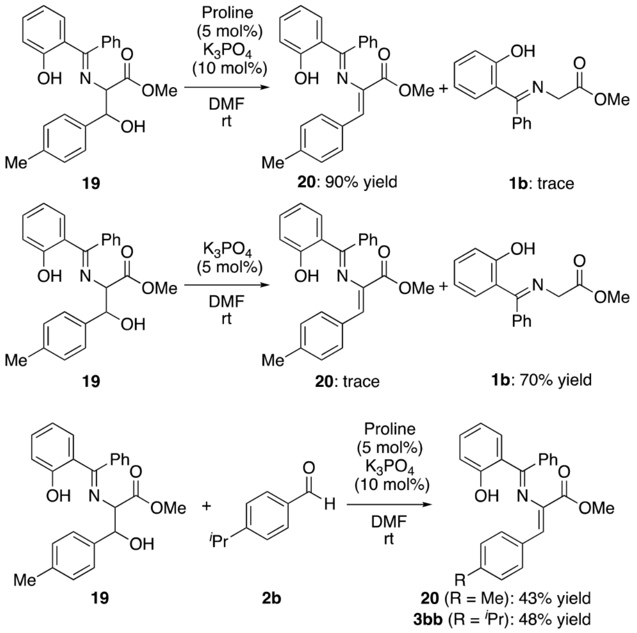
Scheme 4. Deprotection of N-Terminal and Peptide Synthesis



The corresponding dipeptides **11**−**15** were subsequently obtained in high yields without erosion of the enantioselectivity using Fmoc-amino acid chlorides (Scheme 4B). Congested valine could be incorporated into the N-terminal, delivering dipeptide **15** in high yield. Unstable alkyl aldehyde-derived product **3cu** could also be applicable to the present deprotection/amidation sequence without isolation of *N*-unprotected α,β-dehydroamino ester, delivering the dipeptide **16** in high yield. Further amidation of **12** was achieved after deprotection of *tert*-butyl ester, providing tripeptide **17** in high yield (Scheme 4C). Notably, phenylalanine methyl ester could be coupled with the C-terminal of **14**, and tripeptide **18** was obtained in high yield with minimal erosion of the diastereoselectivity, demonstrating that our synthesized α,β-dehydroamino acid derivatives **3** function as a platform to prepare a variety of peptides through not only C-terminal elongation, but also previously challenging N-terminal elongation.

Finally, to confirm the mechanistic insight, several control experiments were performed (Scheme 5). The *α*,*β*-dehydroamino acid product **20** was observed in high yield when aldol product **19** was used as a starting material under optimal conditions. Omission of proline delivered glycine Schiff base **1b** as a major product, indicating that aldol product is prone to undergo retro reaction and *α*,*β*-dehydroamino acid product would not be converted via aldol product. A crossover experiment using **19** in the presence of **2b** provided the products **20** and **3bb** as a mixture, indicating that the reversible aldol reaction would be operative under optimal conditions.

Scheme 5. Control Experiments



The plausible catalytic cycle is shown in Figure 2. Proline carboxylate **I** generated by K_3PO_4 would couple with aldehyde **2**, providing highly electrophilic iminium species **II**. The iminium species **II** would then couple with enolate derived from **1b** to generate **IV**. Next, intramolecular deprotonation by the carboxylate attached to proline followed by elimination would afford product **3** with the generation of proline carboxylate **I**. An aldol adduct **V** generated from **1b** and **2** would promptly undergo retro reaction.

CONCLUSIONS

In conclusion, a general synthetic method for *α*,*β*-dehydroamino acid-derived peptides was developed through the proline-catalyzed aldol condensation reaction. A variety of aldehydes, including readily enolizable aldehydes, could be used, delivering *Z*-configured *α*,*β*-dehydroamino ester derivatives in high yield. The hydroxy group on the benzophenone imine rendered the catalysis with high reactivity and *Z*-selectivity. Furthermore, the synthesized *α*,*β*-dehydroamino ester derivatives could be incorporated into peptides not only at the C-terminal but also at the previously less explored N-terminal. Further efforts of our group will be focused on conformational analysis of the *α*,*β*-dehydroamino acid-derived peptides.

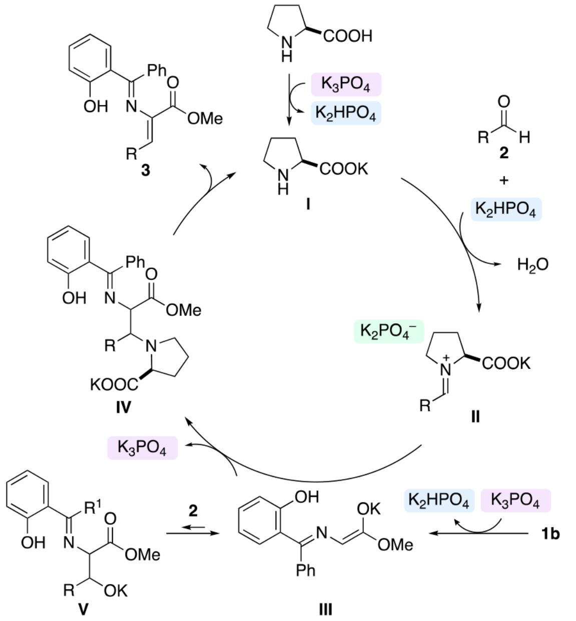


Figure 2. Plausible catalytic cycle.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/prechem.3c00048.

Experimental procedures and spectroscopic data for all new compounds (PDF)

Crystallographic data for *Z*-**3ba** (CIF)

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Notes

The authors declare no competing financial interest.

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(64) A similar ΔG^0 value was observed in DFT calculations of *Z*-**3aa** and *E*-**3aa** (7.72 kcal mol^{-1}). The product *E*-**3ba** was readily isomerized in $CDCl_3$ at room temperature without any catalyst or base, although no isomerization of *E*-**3aa** was observed under the same conditions. Isomerization through an intramolecular oxa-Michael reaction might be operative. See the Supporting Information for details.

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