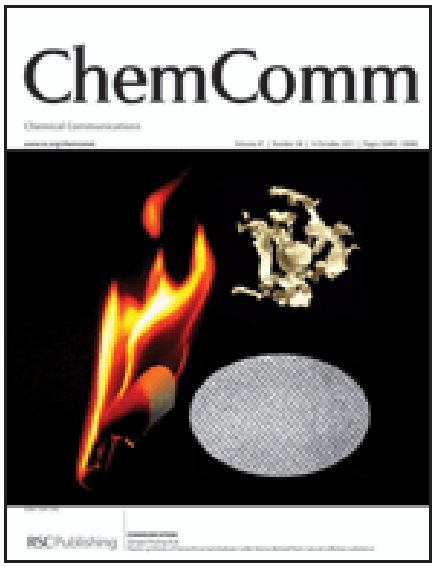

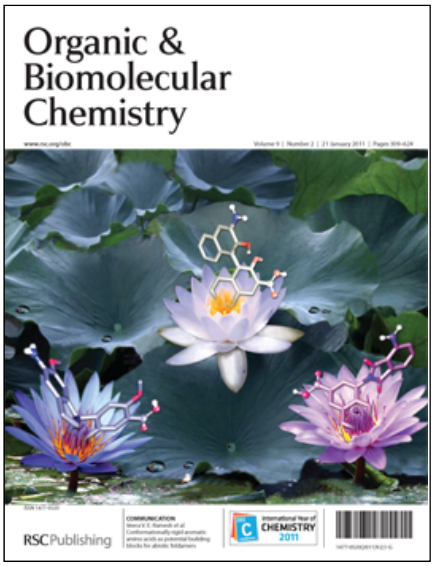

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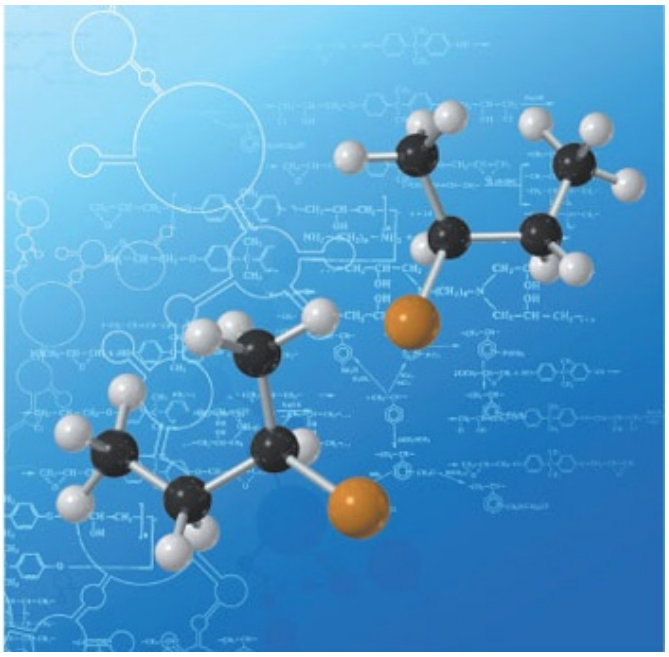

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COMMUNICATION

Asymmetric Michael addition of boronic acids to a γ-hydroxy- α,β-unsaturated aldehyde catalyzed by resin-supported peptide†‡

Kengo Akagawa, Masahide Sugiyama and Kazuaki Kudo*

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A resin-supported peptide catalyst effective for the asymmetric Michael addition of boronic acids to (*E*)-4-hydroxybut-2-enal was developed. From a spectral study, it was revealed that the optimum peptide consisted of both a β-turn and helix. Such a combination of secondary structures was essential for achieving a high catalytic ability.

Recently, peptides have been paid attention to in the field of organocatalysis.[1–3] Peptide catalysts can be considered as simplified enzymes. Enzymes have complicated three-dimensional frameworks consisting of secondary structures such as an α-helix, a β-sheet, and a turn moiety. By combining such structural units, catalytically active reaction sites are constructed, which makes enzymatic reactions highly efficient and stereoselective. Most of the peptide catalysts reported so far are relatively short, thus, it is suspected that the potential of peptide catalysis has not been fully demonstrated. A peptide with multiple secondary structural motifs is expected to have a high catalytic performance.[4]

Our group has developed peptide catalyst **1** for organocatalytic reactions (Fig. 1).[5] Peptide catalyst **1** possesses an N-terminal five residues including a turn motif, D-Pro-Aib (Aib: 2-aminoisobutyric acid),[6] and a helical part. The whole peptide is supported by an amphiphilic resin,[7] which enables efficient synthesis and recovery of the catalyst and facile handling of the peptide with low solubility. In the peptide sequence, both the turn motif and the helical unit are necessary for high enantioselectivity. Especially, it is intriguing that the presence of the helical part significantly improves the stereochemical outcome of the reactions, though this moiety is somewhat distant from the terminal prolyl group which works as the catalytic center. In the organocatalytic reactions performed with peptide catalyst **1**, aromatic aldehydes have been mainly employed, and use of aliphatic aldehydes was limited to those without functional groups. Because the structures and the substituents of peptide chains can be easily modified simply by changing amino acid monomers, it is expected that the substrate scope for peptide-catalyzed reactions can be extended by exploring peptide sequences.

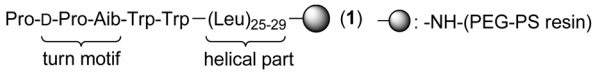
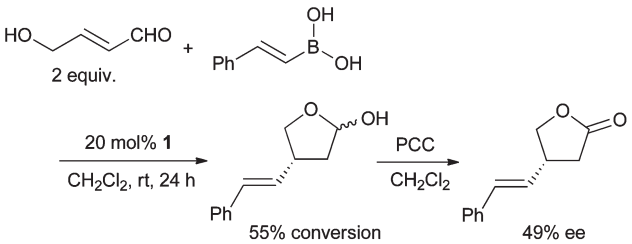


Fig. 1 Resin-supported peptide catalyst.



Scheme 1 Preliminary result with peptide **1**.

The Michael addition to an α,β-unsaturated aldehyde having a hydroxyl group at the γ-position is a versatile reaction to synthesize precursors of β-substituted γ-lactones. Kim[8] reported the Michael addition to (*E*)-4-hydroxybut-2-enal with boronic acids catalyzed by a diarylprolinol silyl ether.[9–11] However, in some cases this reaction suffers low chemical yield and/or quite low enantioselectivity. When peptide catalyst **1** was employed for this type of reaction, only moderate enantioselectivity was attained (Scheme 1). Therefore, we set out an examination to develop a new peptide sequence effective for this reaction and to investigate the structure–activity relationship of the peptide catalysts.

Initially, resin-supported proline was used to test the catalytic ability of the simple prolyl group. The Michael addition of the alkenyl group on the boron atom and the subsequent cyclization proceeded smoothly. However, the corresponding lactone formed by oxidation of the lactol was nearly racemic (Table 1, entry 1).[12] The reaction with the dipeptide D-Pro-Aib, which is known as a turn motif, also gave low enantioselectivity (entry 2). The introduction of another prolyl residue to the N-terminus of this moiety somewhat improved the ee value (entry 3). The same tendency was observed for longer peptides (compare entries 4 and 17). Next, whilst preserving the Pro-D-Pro-Aib sequence,

Institute of Industrial Science, University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8505, Japan. E-mail: kkudo@iis.u-tokyo.ac.jp; Fax: +81 3 5452 6357; Tel: +81 3 5452 6359

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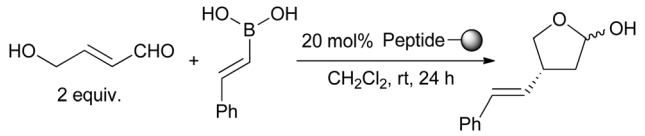
‡ Electronic supplementary information (ESI) available: Experimental details, preparation of peptides and ROESY spectra. See DOI: 10.1039/c2ob25431j

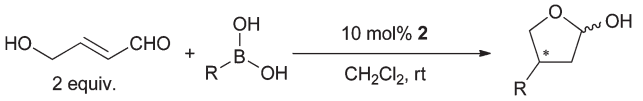
Table 1 Screening of peptide sequence

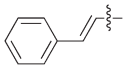
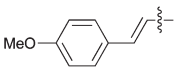
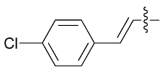
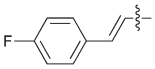
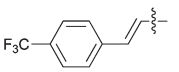
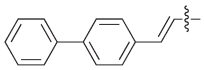
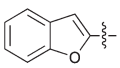


Entry	Peptide	Conversion[a] (%)	ee[b] (%)
1	Pro	72	7
2	D-Pro-Aib	72	−18
3	Pro-D-Pro-Aib	75	37
4	D-Pro-Aib-Trp-Trp	73	−22
5	Pro-D-Pro-Aib-Gly	78	55
6	Pro-D-Pro-Aib-Ala	93	81
7	Pro-D-Pro-Aib-Leu	99	82
8	Pro-D-Pro-Aib-Val	99	71
9	Pro-D-Pro-Aib-Ile	99	70
10	Pro-D-Pro-Aib-Trp	99	74
11	Pro-D-Pro-Aib-Ser	66	72
12	Pro-D-Pro-Aib-$(Gly)_2$	88	64
13	Pro-D-Pro-Aib-$(Ala)_2$	99	82
14	Pro-D-Pro-Aib-$(Leu)_2$	99	83
15	Pro-D-Pro-Aib-$(Val)_2$	99	54
16	Pro-D-Pro-Aib-$(Ile)_2$	99	64
17	Pro-D-Pro-Aib-$(Trp)_2$	85	64
18	Pro-D-Pro-Aib-$(Ser)_2$	72	81
19	Pro-D-Pro-Aib-$(Thr)_2$	46	46
20	Pro-D-Pro-Aib-$(Tyr)_2$	60	76
21	Pro-D-Pro-Aib-$(Cys)_2$	28	58
22	Pro-D-Pro-Aib-$(Ala)_3$	99	80
23	Pro-D-Pro-Aib-$(Leu)_3$	99	81
24	Pro-D-Pro-Aib-$(Val)_3$	79	52
25	Pro-D-Pro-Aib-$(Ile)_3$	72	50
26	Pro-D-Pro-Aib-$(Ser)_3$	63	78
27	Pro-D-Pro-Aib-$(Ala)_4$	99	82
28	Pro-D-Pro-Aib-$(Leu)_4$	99	77
29	Pro-D-Pro-Aib-$(Ala)_5$ (**2**)	99	91
30[c]	**2**	99	90

[a] Determined by ^{1}H NMR analysis of the crude mixture based on consumed boronic acid. [b] Determined by HPLC analysis after oxidation to the corresponding lactone and hydrogenation of the olefin part. [c] Catalyst loading was 10 mol%.

Table 2 Asymmetric Michael addition of boronic acids to (*E*)-4-hydroxybut-2-enal



Entry	R	Time (h)	Isolated yield[a] (%)	ee[b] (%)
1		24	92	90
2		24	90	83
3		36	81	92
4		24	64	92
5		24	67	96
6		24	71	90
7		24	87	37
8[c]		48	84	71
9		36	94	39

[a] Based on the amount of boronic acid. [b] Determined by HPLC analysis after oxidation to the corresponding lactone. In entries 1 to 6, hydrogenation of the olefin part was conducted before the measurement. [c] The amount of aldehyde was 4 molar equiv.

various amino acid residues were introduced at the C-terminus. While the introduction of even glycine improved enantioselectivity (entry 5), other amino acids with diverse sizes and structures of the side chains further enhanced the selectivity (entries 6 to 10). Takemoto *et al.* reported that a thiourea catalyst with a hydroxyl group effectively activates an alkenyl boronic acid for the asymmetric Michael addition to a γ-hydroxy-α,β-unsaturated ketone.[9d] In the case of the peptide catalyst with a serinyl group, selectivity was the same level as those with other amino acids (entry 11). To investigate the effect of elongation of the peptide chain, two amino acid residues were introduced next to Aib (entries 12 to 21). While the peptide with $(Ala)_2$ or $(Leu)_2$ sequences showed an enantioselectivity comparable to that with mono Ala or Leu residue (entries 13 and 14), the insertion of $(Val)_2$, $(Ile)_2$, and $(Trp)_2$ moieties somewhat decreased the selectivity (entries 15 to 17). It is interesting to note that Ala and Leu groups have the α-helical propensity, while Val, Ile, and Trp do not. Further, amino acids with hydroxyl groups or a thiol group were also tested (entries 18 to 21). Among them, the peptide with the $(Ser)_2$ moiety showed the best enantioselectivity (entry 18). Because the level of enantioinduction with this peptide was similar to those with the $(Ala)_2$ and $(Leu)_2$ residues, it was indicated that the hydroxy groups of serines did not play any positive role for controlling the enantioselectivity. The insertion of trimers and tetramers of the amino acid residues between the N-terminal tripeptide and PEG linker showed a similar tendency (entries 22 to 28); the peptides with alanyl and leucinyl groups maintained good enantioselectivity. Interestingly, when penta-alanyl residues were introduced, the highest enantioselectivity was observed (entry 29).[13] With this peptide, the catalyst loading could be reduced from 20 mol% to 10 mol% to afford the product with full conversion and high selectivity (entry 30).

Using the optimum catalyst **2**, substrate scope was examined (Table 2). Styryl-type boronic acids with various substituents on benzene rings gave the products with good to moderate yield in a highly enantioselective manner (entries 1 to 6). A control reaction using 2-(4-chlorophenyl)vinyl boronic acid (*cf.* entry 3) catalyzed by (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (**3**) was sluggish under the same reaction conditions (38% yield and 69% ee after 36 h). This result demonstrates the usefulness of the present peptide catalyst. According to the literature, use of aryl boronic acids as Michael donors affords the products with quite low enantioselectivity.[8a] For example, the ee value of the reaction with 2-furylboronic acid catalyzed by **3** was

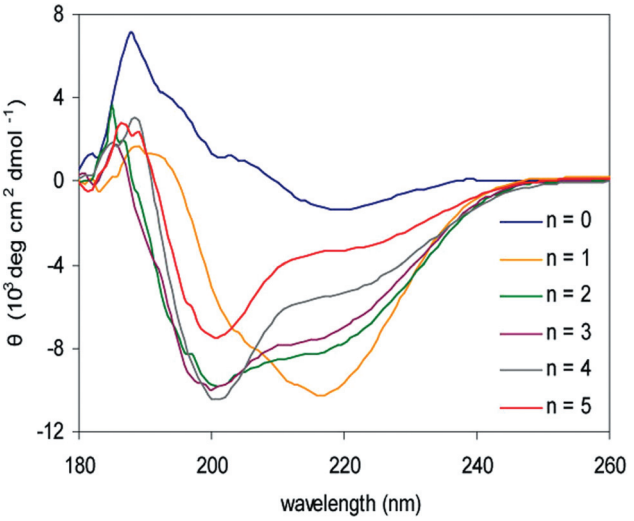


Fig. 2 CD spectra of TFA·Pro-D-Pro-Aib-$(Ala)_n$-NH_2 (n = 0 to 5) in 2,2,2-trifluoroethanol.

reported to be only 4%. With this substrate, the peptide-catalyzed reaction gave the product in a more enantioselective way (entry 7). The reactions with other heteroarylboronic acids also proceeded with higher enantioselectivity than the previous results, though the selectivity left room for improvement (entries 8 and 9).

To obtain information about the structure of peptide catalyst **2**, the spectroscopic analyses of **2**-related peptides were conducted. The circular dichroism (CD) spectra of the peptides having a $–CONH_2$ group at the C-terminus were measured for the sequences of Pro-D-Pro-Aib-$(Ala)_n$ (n = 0 to 5) (Fig. 2).[14] While the spectrum of the peptide with no alanine indicated a lack of any specific secondary structures, the formation of a turn structure was suggested for the one with a single alanyl residue.[15] Incorporation of two or more alanines brought about a further change in the spectra; a negative band at around 200 nm and a shoulder at around 220 nm were observed, implying the formation of a helical structure. Next, two-dimensional NMR spectra were measured for the same set of peptides. The NMR measurements were conducted in $CDCl_3$ for the Pro-D-Pro-Aib-$(Ala)_n$ (n = 0 to 2) sequences. Because of the limited solubility of the peptides with more alanyl residues toward halogenated solvents, the spectra were measured in CD_3CN for the peptides having three and four alanines, and in DMF-d_7 for the one having a pentaalanyl moiety. The ROESY spectra of the peptides with $(Ala)_n$ (n = 1 to 5) residues showed the presence of the NOEs between $C^{\alpha}H$ of Pro and $C^{\delta}H$ protons of D-Pro, and also between $C^{\alpha}H$ of D-Pro and NH of Aib (Fig. 3), while TFA·Pro-D-Pro-Aib-NH_2 did not show these NOE signals (Fig. S1 to S6 in ESI‡). This indicates that the N-termini of the alanine-containing peptides adopt a common secondary structure, possibly a β-turn. It has been reported that the change in the chemical shift of an amide proton upon treatment with polar solvents can be used as an indicator for the formation of a β-turn structure by intramolecular hydrogen bonding.[6a,16] For the peptide TFA·Pro-D-Pro-Aib-$(Ala)_2$-NH_2 in $CDCl_3$, the NH of one alanyl group shifted in a small range ($\Delta\delta$ < 0.2 ppm), whereas the ones of Aib

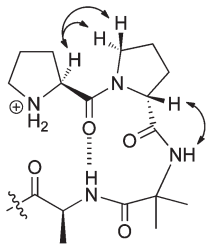


Fig. 3 Schematic illustration of terminal structure.

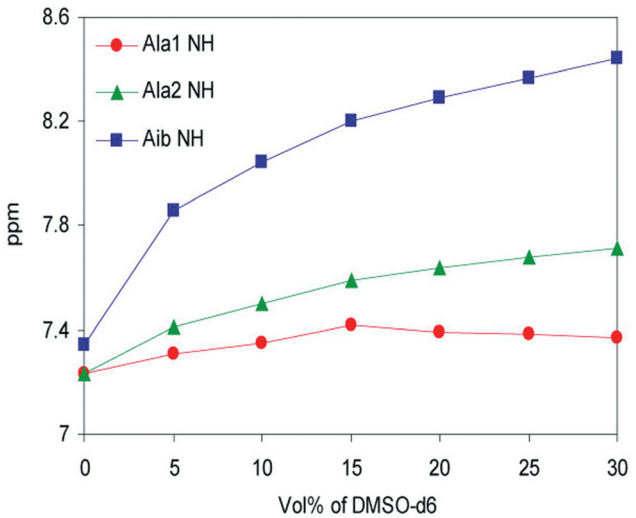


Fig. 4 Chemical shift changes for amide protons of TFA·Pro-D-Pro-Aib-$(Ala)_2$-NH_2 in $CDCl_3$ with DMSO-d_6.

and another Ala shifted significantly ($\Delta\delta$ = 1.2 and 0.5 ppm, respectively) to a lower magnetic field upon addition of DMSO-d_6 (Fig. 4). The small shift of the alanyl amide proton was similarly observed when the peptide with one alanyl group, TFA·Pro-D-Pro-Aib-Ala-NH_2, was employed for the same experiment. This indicates that the amide proton of the alanyl residue is involved in intramolecular hydrogen bonding. From these data together with the CD and ROESY spectra, the peptides with alanyl residues are considered to form a β-turn structure at the N-terminus. The IR spectra of the resin-supported peptides swollen with CH_2Cl_2 afforded information on the structures of them used in the catalytic reaction. The N–H stretching region of the IR spectra for resin-supported Pro-D-Pro-Aib-$(Ala)_n$ (n = 0 to 5) is shown in Fig. 5. For the peptide Pro-D-Pro-Aib, the absorptions with peak tops at around 3350 cm^{-1} and 3420 cm^{-1} were observed. The former peak derives from a hydrogen bonded N–H group and the latter is due to a free N–H group. When one alanyl group was added at the C-terminus of this peptide, the peak top of the absorbance around 3350 cm^{-1} shifted to a lower-energy region and the peak at around 3420 cm^{-1} disappeared. This means that the intramolecular hydrogen bonding is strengthened by the introduction of alanine,[17] which is consistent with the CD and NMR studies in the solution state, and strongly indicates the formation of the β-turn structure. The peptides with more than two alanines at the C-terminus of the Pro-D-Pro-Aib part gave the spectra covering the region around 3300 cm^{-1}.

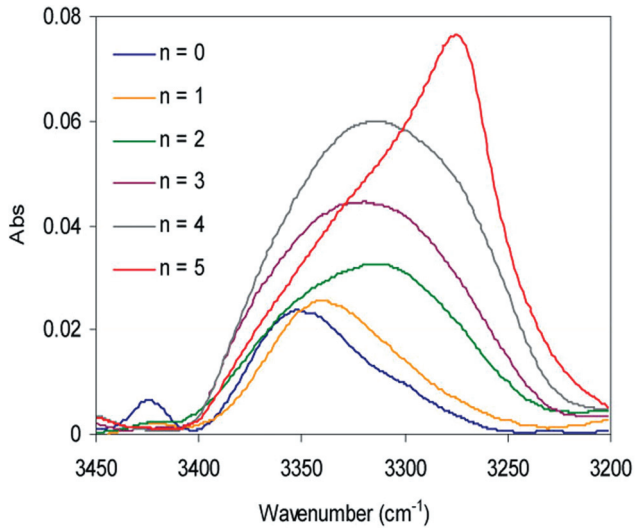


Fig. 5 IR spectra of Pro-D-Pro-Aib-$(Ala)_n$-(PEG-PS resin) swollen with CH_2Cl_2.

Such a change might reflect the formation of a helical structure along with the N-terminal turn structure. The peptide with the pentaalanyl group showed a peak at an even smaller wavenumber. This implies the formation of strong intramolecular hydrogen bonds derived from a robust helical structure. From the observed enantioselectivity with the various peptide catalysts shown in Table 1, it might be safely concluded that not only the presence of the turn structure, but also the helical structure are important for high enantioselectivity. The finding achieved in this paper totally coincides with our recent study on a peptide-catalyzed asymmetric Friedel–Crafts-type reaction in the point that the efficient peptide catalyst should have both an N-terminal β-turn structure and a subsequent helical part.[18] Such a cooperativity of the structural motifs seems interesting and might be applicable to the design of other peptide catalysts, although the interaction between these motifs is waiting to be clarified.

In conclusion, a new resin-supported peptide catalyst effective for the Michael addition to a γ-hydroxy-α,β-unsaturated aldehyde with boronic acids was developed. From spectroscopic analyses, the optimum peptide was indicated to possess both a turn structure and a rigid helical part. The present study demonstrates an example for the creation of an efficient peptide catalyst by combining secondary structural units. This approach might contribute to the advancement in the field of peptide-based organocatalysts.

Acknowledgements

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