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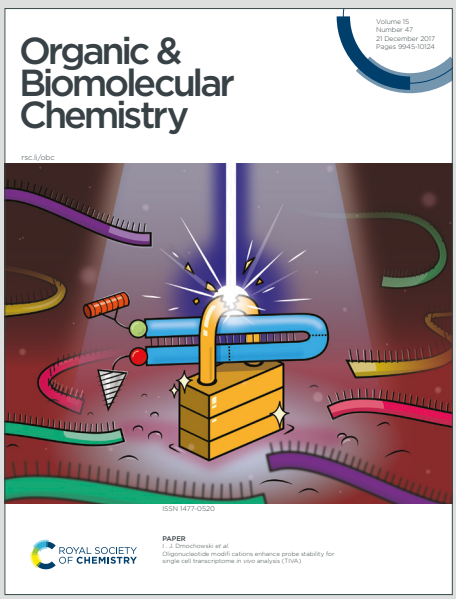

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ARTICLE

N-Primary-Amine Tetrapeptide-Catalyzed Highly Asymmetric Michael Addition of Aliphatic Aldehydes to Maleimides†

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The highly asymmetric Michael addition reaction between maleimides and aliphatic aldehydes catalyzed by low-loading β-turn tetrapeptides with excellent yield and enantioselectivity at room temperature was reported. α-Branched and α-unbranched aldehydes both are suitable nucleophiles. N-aryl, alkyl and hydgogen maleimides all are well tolerated and obtained high yield and enantioselectivity. The transformation can be enlarged to gram-scale without decrease in the yield and enantioselectivity. Furthermore, the succinimide were converted into γ-lactam and γ-lactone, showing good practicality of this work. Some reaction intermediates in the proposed reaction mechanism can be captured with HR-MS method.

Introduction

Chiral succinimide-bearing compounds display significant biological activities, such as antibacterial and antitumor properties.[1] In addition, chiral succinimides are also crucial organic synthetic blocks and can be readily transferred into various biologically and pharmaceutically active compounds.[2] The catalytical asymmetric conjugate addition of nucleophiles to maleimides is a main method to synthesize chiral succinimides.[3] Uniquely, the asymmetric Michael addition reaction of aldehydes with maleimide will produce 1,4-dicarbonyl motif-bearing succinimides, which can be easily transformed into pyrrolidines, γ-lactams and γ-lactones, showing the great significance of this transformation in the asymmetric synthesis.[4] Therefore, the catalytic asymmetric conjugated reaction of aldehydes and maleimides has attracted intense interest to many research groups and numerous successful catalytic methods have been demonstrated with excellent results. The catalysts are mainly organocatalysts, including primary amine-containing thioureas derived from chiral cyclohexane-diamine and amino acids,[5] primary amines,[6] guanidines,[7] imidazoles,[8] squaramide,[9] amino acids and their derivatives.[4b,10] Inspite of these excellent organocatalysts in this asymmetric transformation, other efficient catalytic method is still rare, and thus interesting and anticipated.

Synthetic short peptides are often used as artificial surrogates of natural enzymes in numerous organic transformations for their readily availability, high stability, easy modification and well-tolerance to reaction conditions.[11] A number of peptide-catalyzed highly enantioselective transformations have been demonstrated by groups.[12,13] Recently, even photocatalytic peptides were developed in green organic reactions.[14] To date, however, only two reports on catalytic peptides used as artificial enzymes have been disclosed in this transformation.[4a,15] Wennemers and the co-workers first demonstrated the tripeptide-catalyzed conjugate addition of linear aldehydes as nucleophiles to maleimides with high yield, excellent enantioselectivity and good diastereoselectivity.[4a] Despite the great success of Wennemers's work on this transformation, there is one limitation that the nucleophiles are only restricted to α-unbranched aldehydes. The transformation of α-branched aldehydes as nucleophiles would produce all-carbon quaternary center-bearing succinimides. The all-carbon quaternary center is a common motif in biologically and pharmaceutically active compounds and has always been in the research centre of the organic synthesis.[16] Juaristi and co-workers reported the second cases about synthetic short peptide-catalyzed conjugate addition of aldehydes to maleimides.[15] They employed dendrimeric α,β-dipeptidic conjugates as organocatalysts but the enantioselectivity is not high. Therefore, other synthetic peptides are needed to efficiently catalyze asymmetric reactions of both α-branched and α-unbranched aldehydes as nucleophiles with maleimides.

Recently, our group designed and synthesized a series of tetrapeptides and successfully utilized them to catalyze highly enantioselective aldol reactions,[17] these tetrapeptides are primary amine N-terminus, different from the proline N-terminal tripeptides by Wennemers group. Reportedly, proline and its derivatives are more suitable to catalyze α-unbranched aldehyde nucleophiles,[4a,10b] while primary amine-based organocatalysts are more ideal catalysts for α-branched

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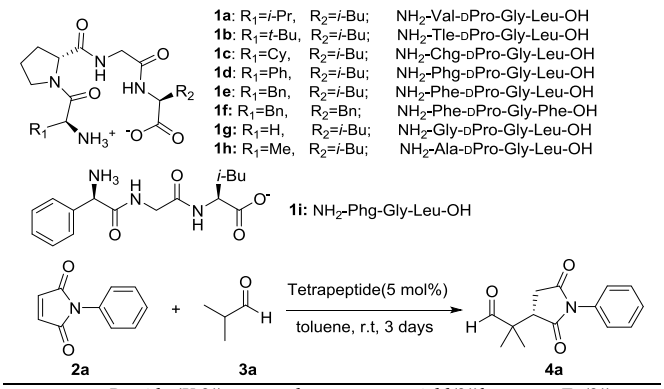
aldehyde nucleophiles in this transformations.[4b,10a] And compared to the α,β-dipeptidic conjugates of Juaristi group, we proposed that the primary amine N-terminal tetrapeptides with a β-turn secondary structure should provide a more ideal sterically restricted chiral environment for this transformation, possibly resulting in a highly asymmetric induction.[18] Intrigued by this proposal, we have explored the tetrapeptide-catalyzed conjugate addition of α-branched and linear aldehydes to maleimides for 1,4-dicarbonyl-bearing succinimides. In this article, we disclose this primary-amine N-terminal and β-turn secondary structural tetrapeptide-catalyzed conjugate transformation with high yield and excellent enantioselectivity under a mild reaction condition for the first time.

Results and discussion

Initially, we screened the tetrapeptide catalysts using *N*-phenylmaleimide and isobutyraldehyde as the model reaction, and found that all tetrapeptides can successfully catalyze the reaction (table 1, entries 1 to 6). Among them, **1d** and **1e** obtained the best results (91% ee) when toluene was used as the solvent. Next, we optimized the solvent using **1e** as the catalyst because it obtained a higher yield than **1d.** Aprotic solvents such as DCM, MeCN, THF, and EtOAc all obtained excellent enantioselectivity (97-99% ee), and MeCN is ideal in view of both yield and enantioselectivity (entry 8). Dichloromethane obtained the highest enantioselectivity but with relatively low yield (entry 7). The use of the protic solvent EtOH caused a significant decrease in enantioselectivity. Next, we tried to reduce the amount of the tetrapeptide. When the amount of tetrapeptide **1e** was reduced by half, the yield and enantioselectivity still kept very high (entries 8 vs 13). Further reducing the amount remarkably deteriorated the yield although the enantioselectivity was not weakened (entries 13-15). Finally, we compared the catalytic effects of **1d** and **1e** under the optimal reaction conditions again, and found that **1d** can provide much higher yield and enantioselectivity than **1e**, thus more suitable to this transformation.

In order to investigate the origin of the stereoselectivity in the transformation, tetrapeptides **1g** and **1h** were prepared and their catalytic activity and asymmetric induction were evaluated. The results show that the two peptides obtained reduced enantioselectivity in comparison with tetrapeptide **1d** (entries 16 vs 17-18). But interesting results were viewed. Tetrapeptide **1g**, even with an achiral N-terminal glycine, still realized 90% yield and 72% enantioselectivity, indicating the enantioselectivity determined by both the chirality of the N-terminal amino residue and the secondary structure of the peptide (entry 17). This result is further verified by tetrapeptide **1h** with an N-terminal alanine, the smallest natural chiral amino acid but with highly increased enantioselectivity to 97%. Combining these two examples and the tetrapeptide **1d**, we believe that the spatial structure of the tetrapeptide and the properties of the N-terminal amino acid cooperatively determine the stereoselectivity for this asymmetric transformation. We propose that the superior enantioselectivity of these tetrapeptides to the reported α,β-dipeptidic conjugates is mainly due to the peptide secondary structure.[15]

Table 1 Optimization of reaction conditions. [a]



entry	Peptide (X %)	solvent	yield(%)b	Ee(%)c
1	**1a** (5%)	toluene	35	77
2	**1b** (5%)	toluene	29	72
3	**1c** (5%)	toluene	38	41
4	**1d** (5%)	toluene	43	91
5	**1e** (5%)	toluene	55	91
6	**1f** (5%)	toluene	43	85
7	**1e** (5%)	CH_2Cl_2	80	99
8	**1e** (5%)	MeCN	93	98
9	**1e** (5%)	EtOH	91	88
10	**1e** (5%)	THF	90	97
11	**1e** (5%)	DMSO	--	--
12	**1e** (5%)	AcOEt	90	98
13	**1e** (2.5%)	MeCN	95	98
14	**1e** (1%)	MeCN	56	98
15	**1e** (0.5%)	MeCN	trace	--
16	**1d** (2.5%)	MeCN	98	99
17	**1g** (2.5%)	MeCN	90	72
18	**1h** (2.5%)	MeCN	91	97
19	**1i** (2.5%)	MeCN	67	38

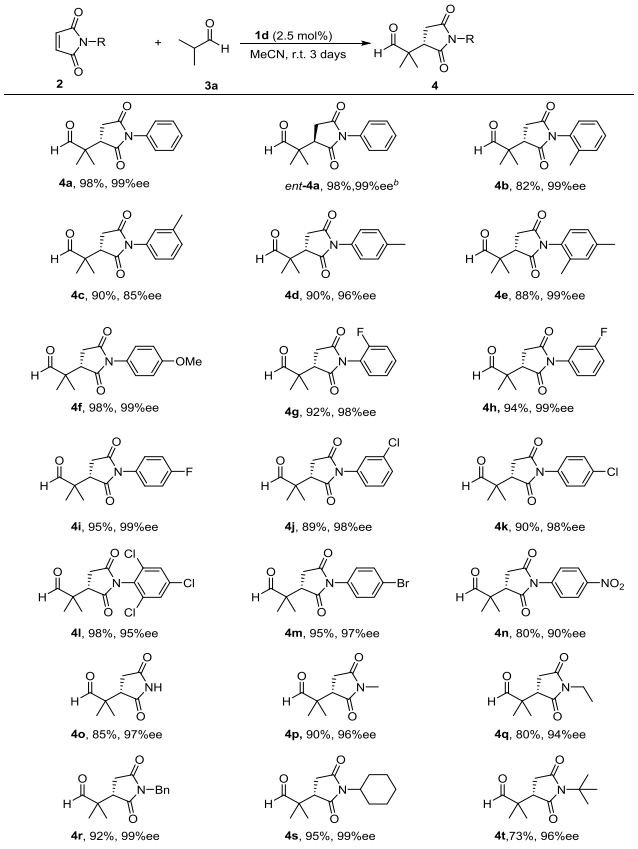
[a]0.5 mmol of **2a**, 1.0 mmol of **3a** and 1 mL solvent were used. [b]Isolated yield was reported. [c]ee was determined by chiral HPLC. The configuration was assigned by comparing the optical rotation direction of **4a** with its reported datum.[5b]

To further show the significance of the peptide secondary structure in the catalytic transformation, tripeptide **1i** without the D-proline residue was prepared. The dipeptide D-Pro-Gly is a crucial unit to form β-turn and β-hairpin secondary structures in short peptides.[19] Without proline residue, tripeptide **1i** cannot form secondary structure, obviously. Just as prediction, it only achieved sharply decreased 67% yield and 38% enantioselectivity, strongly showing indispensability of the proline residue in the peptides and the importance of the peptide secondary structure in the catalytic asymmetric reaction.

With the optimized reaction conditions in hand, we explored scope of maleimides bearing different N-protecting groups with isobutyraldehyde (Table 2). With a yield up to 98% (**4a**, **4f**, **4l**) and ee up to 99% (**4a**, **4b**, **4e, 4f**, **4h**, **4i**, **4r**, **4s**), The results

show that succinimides can be obtained always in high yield and excellent enantioselectivity whether the aryl group on N-atom is electron-deficient or electron-rich. In addition, unprotected maleimide can directly obtain N-protection-free succinimides, which avoids the additional steps to deprotect the protecting groups and thus represents the economic procedure to optically active succinimides.[20] In this work, the N-protection-free maleimide also successfully obtained high yield and enantioselectivity (**4o**). Furthermore, N-alkylated maleimides (**4p**, **4q**, **4r**, **4s**, **4t**) can similarly smoothly achieve 94-99% excellent enantioselectivity with varied yield from 73-95%. The sterically-restricted N-terbutyl maleimide resulted the lowest 73% yield but with high 96% enantioselectivity (**4t**). At last, high yield and enantioselectivity enantiomer of succinimide **4a** was also obtained (**4a** vs. *ent*-**4a**) when *ent*-**1d** (the enantiomer of tetrapeptide **1d**) was used. Therefore, pairs of enantiomers can be readily accessible by simply switching a pair of tetrapeptide enantiomers with each other.

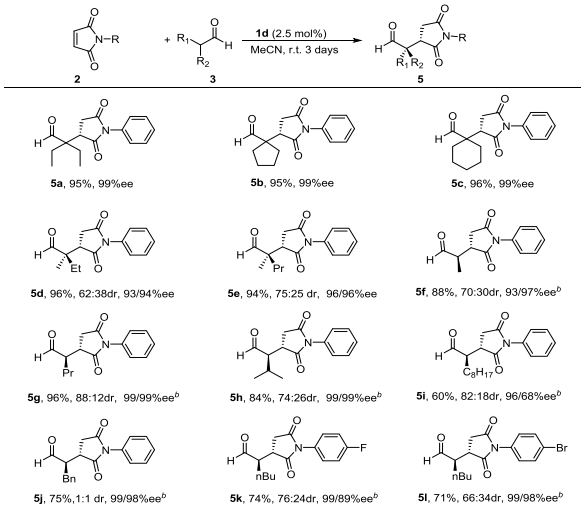
Table 2 Explorer of maleimide with different N-protecting groups.[a]



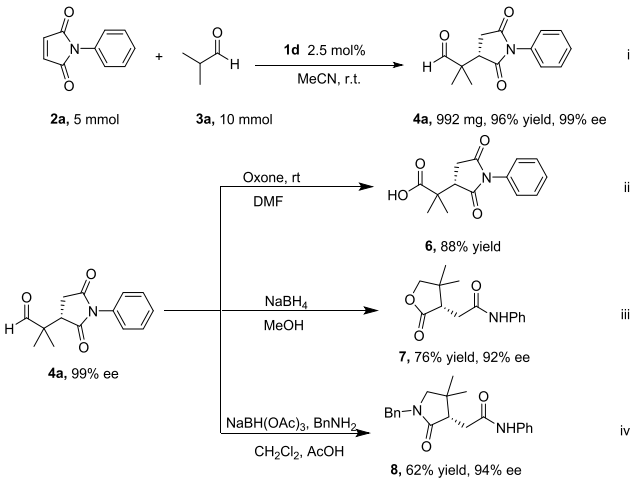
[a]0.5 mmol of **2**, 1.0 mmol of **3a** and 1 mL MeCN was used. Isolated yield was reported. ee was determined by chiral HPLC.[b] *ent*-**1d** was used.

Next, the scope of the aldehydes was explored and the results are shown in Table 3. First, symmetrical α-branched aldehydes were observed; high yield and uniformly excellent 99% enantioselectivity were obtained (Table 3, **5a**, **5b** and **5c**). Second, asymmetric α-branched aldehydes were evaluated and all of them obtained succinimides **5d** and **5e** of exocyclic linear all-carbon quaternary stereocenter with high yield, excellent enantioselectivity and moderate diastereoselectivity (up to 3:1). Finally, a series of linear aldehydes were investigated and they also smoothly obtained succinimides in good to high yield, excellent ee and moderate diastereoselectivity (**5f** to **5l**), showing well suitability of the tetrapeptide to aliphatic aldehydes. In spite of this, while comparing to the uniformly high yield from α-branched aldehydes in this transformation, the good to high yield from α-unbranched aldehydes shows that N-primary amine terminal tetrapeptide is more suitable to α-branched aldehydes. Therefore, this work is a good supplementary counterpart to Wennemers' N-prolyl tripeptides in this transformation.[4a]

Table 3 Michael addition reaction with **2** and **3**.[a]



[a]0.5 mmol of **2**, 1.0 mmol of **3** and 1 mL MeCN were used. Isolated yield. ee and dr value were determined by chiral HPLC and the reported ee is anti/syn. [b]10% **1d** was used. The configuration was assigned by comparing the optical rotation direction of **5e** with its reported datum.[4b]



Scheme 1 Transformations of the Michael Addition Product **4a**

To display the practicality of this work, the model reaction of isobutyraldehyde and N-phenylmaleimide was successfully enlarged to gram scale without reducing yield and enantioselectivity (i, Scheme 1). Furthermore, succinimide **4a** can be readily oxidized to acid **6** with oxone (ii), reduced into lactone **7** with $NaBH_4$ (iii), and transferred into lactam **8** with $NaBH(OAc)_3$ and $BnNH_2$ by reductive amination (iv). These derivatives all are crucial intermediates for biological active molecule synthesis.[1,2]

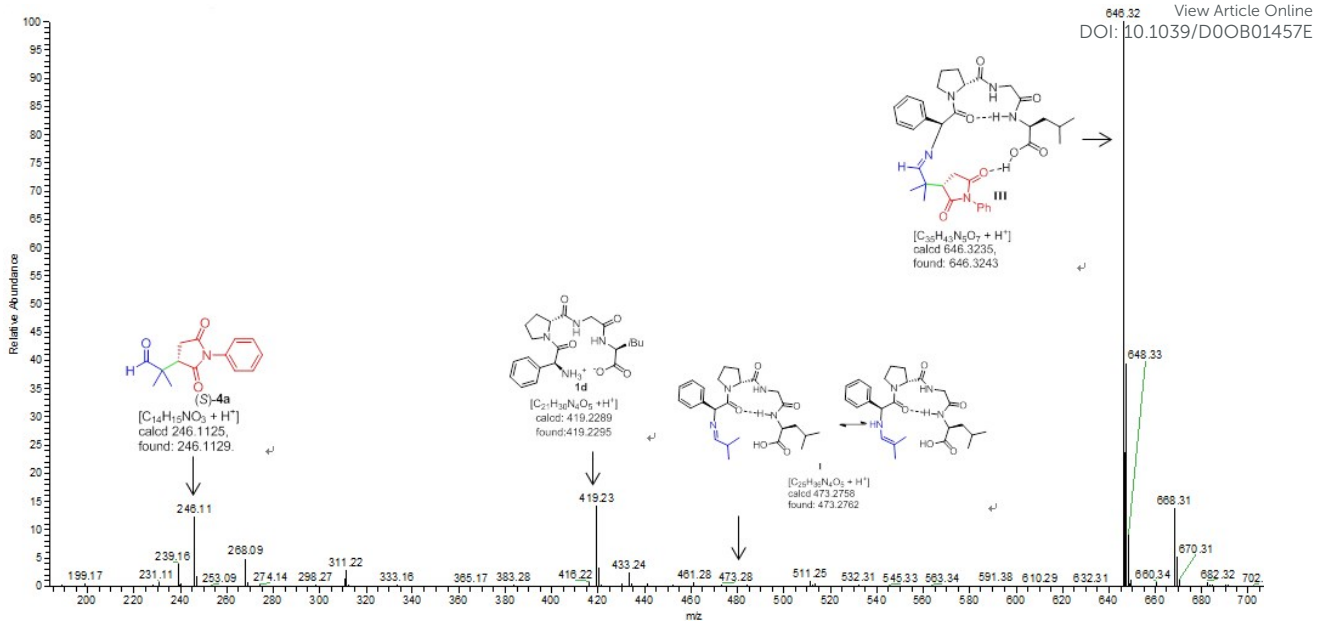
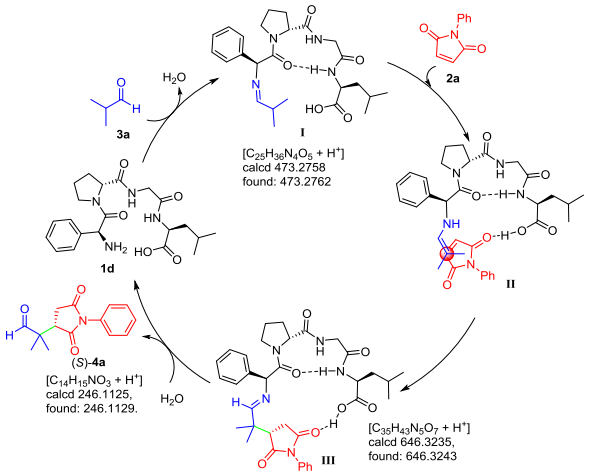


Figure 1 Intermediate captured by HR-MS



Scheme 2 Proposed activation and reaction mechanism

To explore the reaction mechanism, we tried to capture the intermediates of the transformation in situ by using the HR-MS method. Figure 1 shows that the reaction mixture includes the intermediate **I** or its enamine form generated from tetrapeptide **1d** with isobutyraldehyde, intermediate **III** formed by tetrapeptide **1d** with succinimide **4a**, the product succinimide (*S*)-**4a** and tetrapeptide **1d**. This result clearly indicates that the reaction undergoes possibly following the enamine intermediate process. Based on such an investigation and previous reports,[6a] we speculate that the possible reaction process in Scheme 2. Tetrapeptide **1d** first combines isobutyraldehyde in situ to form imine **I**. Imine **I** can reversibly change into reactive and nucleophilic enamine **II**. Enamine **II** then reacts with maleimide, which is activated by the terminal -COOH group of the tetrapeptide via H-bond formation between H-atom of the -COOH from the peptide and the O-atom of the carbonyl group from maleimide. The attack of the enamine to maleimide occurs in the *Si*-face of maleimide, realeasing (*S*)-succinimide **4a**. The special spatial conformation and steric effect of β-turn tetrapeptide **1d** well determines the attacking direction and thus leads to high yield and excellent enantioselectivity of the conjugate reaction.

Conclusions

In summary, we have developed the first N-primary amine terminal β-turn tetrapeptide-catalyzed highly enantioselective conjugate addition aliphatic aldehydes to maleimide with high yield and excellent enantioselectivity. N-arylated and alkylated maleimides all are suitable substrates and achieved high yield and excellent enantioselectivity. Even the N-protection-free maleimide is well-tolerated with no reduction of the yield and enantioselectivity. α-Branched and unbranched aldehydes are both compatible to the tetrapeptide although the α-branched aldehydes obtained higher yield in some cases. Compared to the reported organocatalysts, less amount of the tetrapeptide can achieve high yield and excellent enantioselectivity in this work. The reaction can be successfully enlarged into gram-scale and the yield and enantioselectivity are not deteriorated. The yielded succinimide can be transformed into some crucial synthetic intermediates for bioactive compounds. The reaction possibly follows the enamine-based mechanism and the key intermediates can be investigated using HR-MS method.

Conflicts of interest

There are no conflicts to declare.

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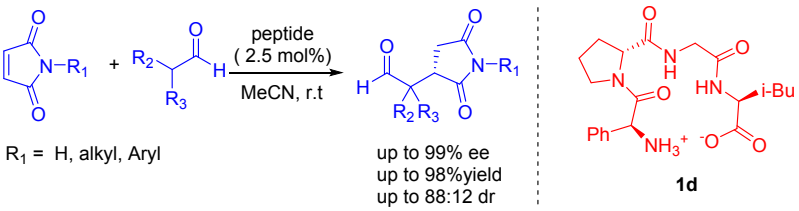

The highly asymmetric Michael addition reaction between maleimides and aldehydes catalyzed by *N*-Primary-Amine β-turn tetrapeptides with excellent yield and enantioselectivity was reported.