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NOVEL OCTAPEPTIDE AS AN ASYMMETRIC CATALYST FOR MICHAEL REACTION IN AQUEOUS MEDIA

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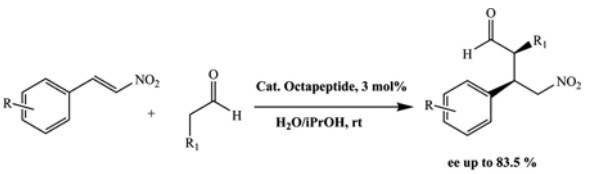
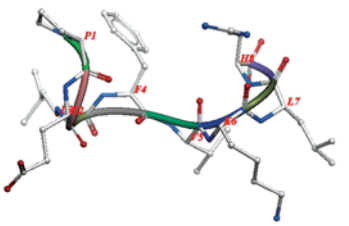
[5]*Structural and Synthetic Biology Research Centre, Malaysia Genome Institute, Jalan Bangi, Kajang, Selangor Darul Ehsan, Malaysia*

GRAPHICAL ABSTRACT





Abstract *In this work, three forms of a novel octapeptide have been evaluated as asymmetric catalysts for the Michael reaction. Low quantity catalyst loading, ecofriendly solvents, and*

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Address correspondence to Mohd Basyaruddin Abdul Rahman, Faculty of Science, Universiti Putra Malaysia, 43400 UPM, Serdang, Selangor, Malaysia. E-mail: basya@upm.edu.my

reusability of organocatalyst successfully applied to attain excellent yields and moderate enantioselectivities in the Michael reaction.

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resources: Full experimental and spectral details.]*

Keywords Asymmetric; enantioselectivities; Michael reaction; octapeptide; organocatalyst; reusablity

INTRODUCTION

The Michael reaction is a crucial method for the creation of carbon–carbon bond frameworks in organic synthesis. In recent decades, asymmetric Michael addition reactions have undergone significant progress using chiral metal complexes and free metal organocatalysts.[1,2] Recently, short peptides have been established as excellent asymmetric catalysts for a number of enantioselective organic synthesis reactions including conjugate additions,[3] acylation reactions,[4] hydrocyanation of aldehydes[5] and imines,[6] phosphorylation,[7] and Baylis–Hillman[8] and direct aldol[9] reactions. In many cases, to accomplish good diastereoselectivity and enantioselectivity in a reaction, typically 10–30 mol% of asymmetric organocatalysts is required.[10] Hence, the low amount of catalyst loading with high stereoselectivity and applications for a broad range of substrates has remained a formidable challenge for the development of asymmetric organocatalysts. In this context, an octapeptide catalyst scaffold was designed and synthesized based on the hydrophilicity, flexibility, and rigidity of the peptide structure to establish whether the residue would provide a catalytically active substructure. This article reports the discovery of a novel octapeptide and its derivatives as asymmetric organocatalysts for the Michael addition reaction as shown in Fig. 1. Most enzymes have multiple functional groups in their active site, which have been placed in appropriate positions. When those multiple functional groups work together, the enzyme can perform catalytic activity. Peptides can be an ideal compromise between small rigid organocatalysts and enzymes. To design this octapeptide, aldo-ketoreductase enzyme was considered. Asp47, Lys77, His110, and Tyr52 with side-chain functional groups play key roles in active site of aldo-ketoreductase enzyme.[11] Therefore, Asp, Lys, and His were utilized to synthesize octapeptide **1** (Fig. 1). Herein, we report an investigation of the potential of peptide **1** with eight amino acids, and its different forms **1a** and **1b** (Fig. 1), as organic catalysts for the Michael reactions. The reactions were carried out with various aldehydes and ketones in the presence of three forms of octapeptide: (I) the octapeptide supported by Rink amide-Am-resin with side-chain protection **1a** to determine whether side-chain groups have any significant role to enhance enantioselectivity, (II) deprotected side-chain protection groups linked to the resin **1b**, and (III) Octapeptide **1** cleaved from the resin and without side-chain protection groups in aqueous media.

Recovery of organocatalysts from reaction mixtures and their recyclability are highly desired because most organocatalysts are expensive and have lengthy synthesis procedures. Therefore, we recovered our asymmetric catalyst and investigated its activity and enantioselectivity in the Michael reaction.

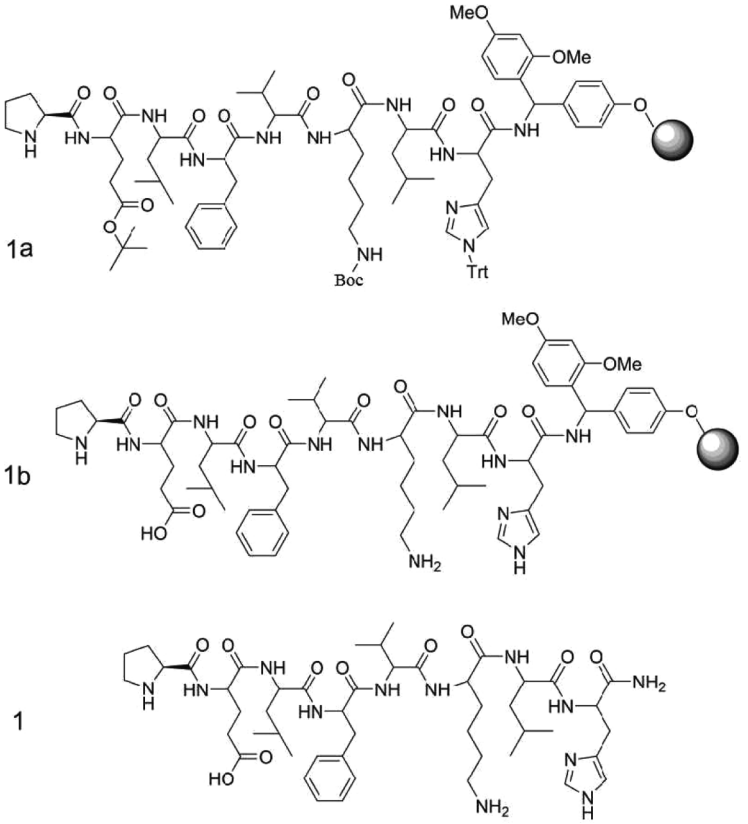


Figure 1. (**1a**) Protected octapeptide attached to Rink-Amide-Am-Resin. (**1b**) Octapeptide without side chain protection group but attached to the resin. (**1**) Cleavage peptide from resin.

RESULTS AND DISCUSSION

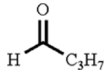
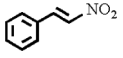
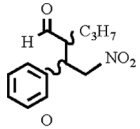
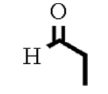
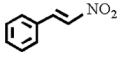
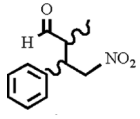
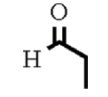
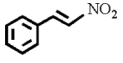
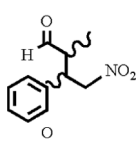
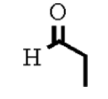
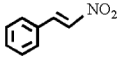
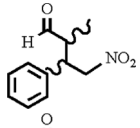
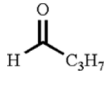
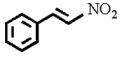
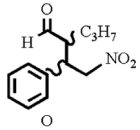
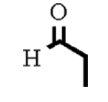
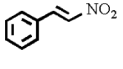
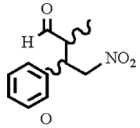
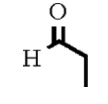
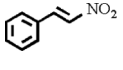
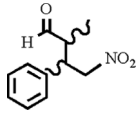
In this research, the design of new octapeptides to catalyze a carbon–carbon bond-forming reaction like the Michael addition to create a high degree of diastereoselectivity and enantioselectivity involving computational and experimental procedures was performed. Michael addition reactions of nitrostyrenes with aldehydes and ketones have been found to be some of the most important and efficient methods for the preparation of γ-nitrocarbonyl compounds.[12]

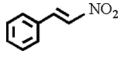
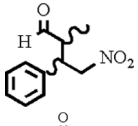
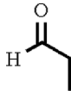
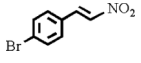
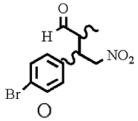
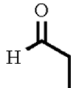
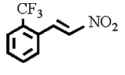
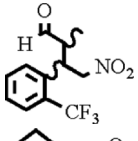
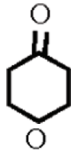
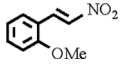
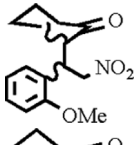
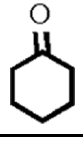
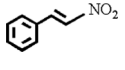
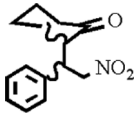
To prove this hypothesis, we synthesized and evaluated octapeptide with three forms in Michael reactions: (I) Octapeptide **1a** was synthesized to investigate the role of hydrogen bonding and steric hindrance in enhancement of regio- and enantioselectivity. Thus, a peptide was attached to the resin without removing side-chain protection groups. (II) Octapeptide **1b** was prepared from **1a** by using 10% HCl/dioxane to remove side-chain protection groups. Using **1b** in the Michael reactions demonstrates the role of hydrogen bonding in enhancement of enantiomeric excess. (III) Octapeptide **1** displays whether or not the flexibility would increase enantio- and diastereoselectivity. The Michael reaction was performed between nitrostyrene

and propanal in $^{i}PrOH/H_2O$ (0.5 ml / 0.5 ml) in the presence of **1a** at room temperature within 72 h. Because of the rigidity and steric hindrance of octapeptide **1a**, the enamine intermediate could not form. Therefore, hydrogen bonding between the carboxylic acid group of glutamic acid and the nitro group could not occur.[13–15] As a result, no product was obtained (Table 1, entries 6 and 7). Improvement of the reaction efficiency in terms of both yield and overall selectivity was considered by removing the side-chain protection groups without cleavage of the octapeptide from the resin **1b** (Fig. 1). For this purpose, HCl/dioxane (10% w/v) was used to remove the *tert*-butyl, Boc, and trityl groups at ambient temperature within 30 min. Nitrostyrene with propanal in the presence of catalyst **1b** in $^{i}PrOH$ as the solvent (Table 1, entry 4) was reacted at ambient temperature within 24 h. When catalyst **1b** was employed under the aforesaid conditions (Table 1), an excellent isolated yield and low enantioselectivity were observed (Table 1, entry 3, 25.9% ee). Interestingly, the yield (either isolated or ee%) was increased when steric hindrance was reduced by removing the side-chain protection groups. The reaction was also catalyzed by **1b** in different solvents. It is also interesting to note that changing the solvent to a more polar solvent remarkably increased the ee. In Table 1, entry 4, $^{i}PrOH/H_2O$ (1:1) was utilized instead of $^{i}PrOH$ and the enantioselectivity increased from 25.9% to 44.7%. This may be due to enhanced solubility and increased flexibility of the peptide attached to the resin. Although this first successful catalytic asymmetric Michael reaction represented a significant advance in asymmetric synthesis, there were some drawbacks to the method because of low ee. In an effort to address this problem, we obtained catalyst **1** from **1a** by using a suitable scavenger, which comprised trifluoroacetic acid (TFA, 92.5%), triisopropylsilane (2.5%), 1,4-dithiothritol (2.5%), and water (2.5%), by agitation for 2 h to separate peptide from resin. Peptide **1** with high purity (97%) was obtained. When catalyst **1** was used in the Michael reactions, enantioselectivity improved significantly. The results are summarized in Table 1. The flexibility of the peptide allowed the formation of a better enamine intermediate. Moreover, hydrogen bonding between the nitro group of nitrostyrene and the -COOH and -NH groups of the octapeptide is an additional force to keep nitroolefins on one side of catalyst and nucleophile has to attack of the opposite side. Because of this reason, an improvement in the stereoselectivity was observed (Scheme 2)[16–18] In our next screening experiments, the asymmetric Michael addition of valeraldehyde to nitrostyrene catalyzed by **1** was chosen as the model reaction (Scheme 1). The reaction was performed in an ecofriendly aqueous medium $^{i}PrOH/H_2O$ at room temperature with catalyst loading of 3 mol% and one drop of *N*-methylmorpholine (NMM) as a pH adjustment reagent (pH = 5–5.5). As shown in Table 1, in the presence of low quantity loading of catalyst **1**, good yield of the reaction (87%), diastereomeric ratio (dr = 84/16), and moderate enantiomeric excess (45%) were obtained within 24 h (Table 1, entry 1). The enantioselectivity was significantly decreased when long-chain aldehydes were used (Table 1, entry 1, 45% ee). This was most probably due to increased steric hindrance between the aldehyde and the peptide, which inhibited the creation of the enamine intermediate.

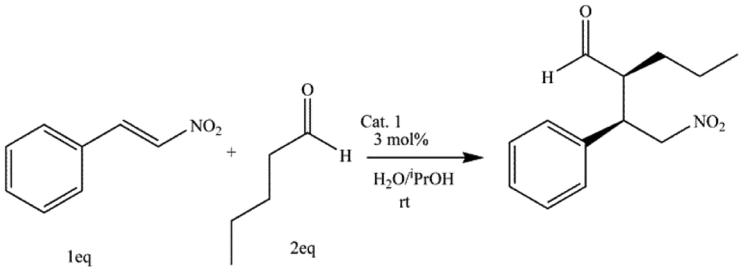
To further investigation, the scope and limitations of the Michael reactions between a variety of aldehydes and ketones with nitroolefins catalyzed by peptide **1** were also examined. The reaction between propanal and nitrostyrene (Table 1, entry 2) exhibited significantly greater yield (95%) and moderate enantioselectivity

Table 1. Michael addition in the present of different substrates and catalysis[a]

Entry	Sub. 1	Sub. 2	Product	Cat. (Mol%)	Solv.	Time (h)	Yield (%)[b]	dr (%)[c]	ee (%)[syn][d]
1				**1**(3)	$H_2O/^iPrOH$	24	87	84/16	45
2				**1**(3)	$H_2O/^iPrOH$	24	95	80/20	62.7
3				**lb** (5)	^iPrOH	24	100	91/9	25.9
4				**1b**(5)	$H_2O/^iPrOH$	24	100	90/10	44.7
5				**1a**(10)	$H_2O/^iprOH$	72	N.R	–	–
6				**1a**(10)	$H_2O/^iPrOH$	72	N.R	–	–
7				**L**-Proline (3)	$H_2O/^iPrOH$	72	65	60/40	0

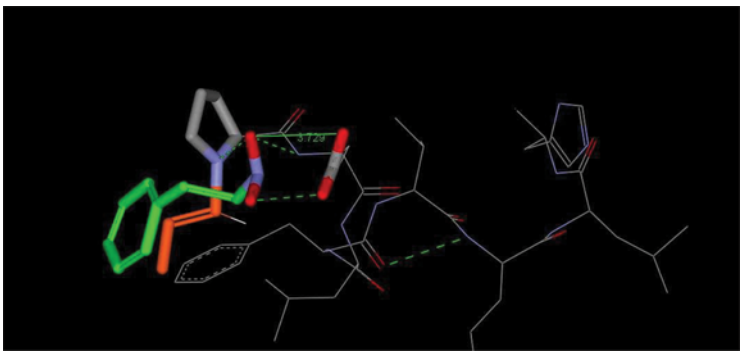
8				**1**(3)[e]	$H_2O/^iPrOH$	5	100	84/16	10
9				**1**(3)	$H_2O/^iPrOH$	24	85	60/40	49.3
10				**1**(3)	$H_2O/^iPrOH$	24	80	83/17	83.5
11				**1**(3)	$H_2O/^iPrOH$	24	87	95/5	72.3
12				**1**(3)	$H_2O/^iPrOH$	24	85	84/16	61.5

[a]Reaction were performed with aldehydes or ketones (2eq) and nitroolefins (1eq), solvents (0.5 ml:0.5 ml), NMM (1 drop to adjust pH = 5–5.5), at RT.
[b]Isolated yield of mixture of syn/anti based on nitrostyrene. Diastereomeric ratio, determined by ^{1}H NMR.
[c]Enantiomeric excess, determined by chiral-phase HPLC analysis.
[d]Diisopropylethylamine (to adjust pH = 5–5.5).

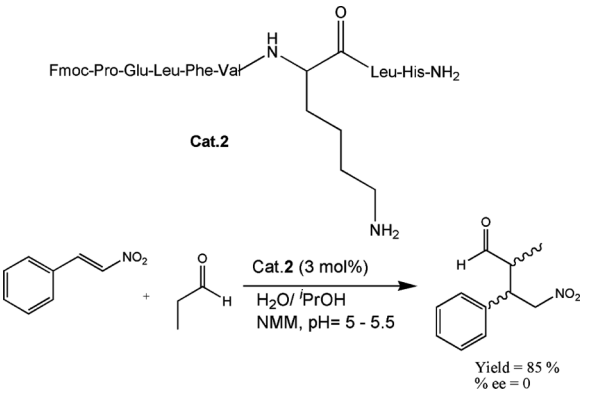


Scheme 1. Michael reaction in the presence of asymmetric catalyst.

(62.7%), albeit roughly similar diastereoselectivity compared to valeraldehyde (Table 1, entry 1). This reaction was performed in the presence of *N,N*diisopropylethylamine (DIEA) to adjust the pH to 5–5.5. This additive increased the reaction rate and yield remarkably but decreased enantioselectivity sharply to 10% (Table 1, entry 8). We have investigated the reactions using a variety of nitrostyrenes as the substrates under the mentioned reaction conditions and the results are summarized in Table 1. An enhancement in enantioselectivity was observed up to 83.5% (Table 1, entry 10). Having electron-donating and electron-withdrawing substituents on the aromatic ring resulted good isolated yield and moderate to good enantioseletivities (Table 1, entries 9–12). Most of the nitroolefins, especially ortho substitution ones, were obtained with good enantioselectivities (Table 1, entries 10 and 11) and with good to excellent diastereoselectivity (83:17 and 95:5 respectively). The ability of the octapeptide and L-proline to serve as the catalyst was compared in the Michael reaction under similar conditions. As shown in Table 1, L-proline did not show any enantioselectivity (Table 1, entry 7). We sought to employ oligopeptides as catalysts in these reactions with the hypothesis that hydrogen-bonding amino acid side chains could aid in transition-state organization.[13–19] Peptides have been shown to be effective catalysts for a range of chemical reactions and provide quick access to libraries that can be tailored to individual synthetic transformations.[18]



Scheme 2. Proposed transition state models for the enantioselectivity of octapeptide **1**. Accelrys DS Visualizer software was applied to draw the mechanism. (Figure is provided in color online.)

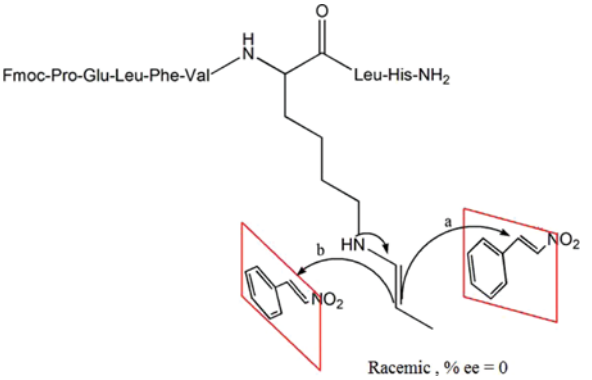


Scheme 3. Michael reaction as a model catalyzed by catlyst 2.

In the structure of octapeptide there are two free amine groups: proline as a secondary amine and lysine as a primary amine. To obtain better insight into the mechanism of the transition state, we performed the Michael reaction by using catalyst 2 (Scheme 3). Catalyst 2 is an octapeptide, in which its proline has been protected by the Fmoc group and lysine side chain is free. Nitrostyrene with propanal in the presence of catalyst **2** in $^{i}PrOH/H_2O$ as the solvents was reacted at ambient temperature within 24 h (Scheme 3).

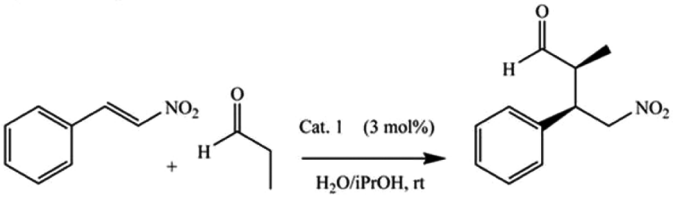
Interestingly, racemic product was obtained. This result signifies that both secondary amine and primary amine (proline and lysine) can catalyze the Michael reactions, but the free amine in the side chain of lysine produces racemate product.[20] According to the proposed mechanism (Scheme 4), it was found that free primary amine located in the side chain of lysine decreases the ees.

We then probed the feasibility of performing the asymmetric catalytic reaction in an ecofriendly solvent. For this purpose, important aspects such as the recyclability of the catalyst and its ability to give forth high product yield and enantioselectivity were investigated. The reaction of *trans*-β-nitrostyrene and propanal under the standard



Scheme 4. Proposed mechanism of free amine group of lysine side chain in the Michael reaction. (Figure is provided in color online.)

Table 2. Reusability studies of ocatapeptide 1 catalyzed Michael addition reaction between trans-β nitrostyrene and propanal under standard reaction conditions



Run	Cat.	mol (%|	Time [h]	yield[%]	ee [%]
1	1	3	24	95	62.7
2	1	3	24	95	60
3	1	3	24	93	58
4	1	3	24	90	56
5	1	3	24	90	55

reaction conditions was chosen as the model to examine the recyclability of the octapeptide catalyst **1**. After the reaction was completed, the reaction mixture was concentrated and the residue was extracted twice with ethyl acetate. Because catalyst **1** was insoluble in ethyl acetate, it could be easily isolated for reuse. As shown in Table 2, catalyst 1 could be recycled and reused at least five times without noteworthy loss of activity.

To design the structural octapeptide of aldo-ketoreductase, prostaglandin F synthesis (PBD, 1VBJ) was considered. The active site of this enzyme consisted of Asp47, Lys77, His110, and Tyr52, which are essential in catalyzing the reaction. Therefore, the octapeptide was designed with eight amino acids that included His, Lys, and glutamic acid. The sequence of this peptide was Pro-Glu-Leu-Phe-Val-Lys-Leu-His-NH_2 which was predicted by LOMETS (Local-MEta-Threading-Server) as a random structure. All amino acids have L configuration. Synthesis and purification of the octapeptide were carried out according to the Fmoc solid-phase strategy.

CONCLUSION

In summary, we present an octapeptide as an asymmetric catalyst in the Michael reaction in ecofriendly media. Low loading of this peptide provided good diastereoselectivity (*syn*/*anti* ratio up to 95:5) and good enantioselectivity (up to 83.5%). This octapeptide was easily recycled and reused up to five times without significant loss of ability to influence the reactivity and enantioselectivity of the Michael reaction.

EXPERIMENTAL

All chemicals were purchased and used without further purification. Analytical thin-layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica-gel plate (0.2-mm thickness). Flashchromatography was performed using

Merck silica gel 60 (70–230 mesh). NMR data were recorded on a 500-MHz NMR (Jeol JNM ECA) spectrometer. The relative and absolute configurations (dr) of the Michael adducts were determined by comparison with ^{1}H NMR spectroscopic analysis. Enantioselectivity were determined by high-performance liquid chromatography (HPLC; Waters 1525 Binary Pump and UV-water 2489) analysis employing a Daicel ChiralPak OD-H, AD-H, and (R,R)WHELK-O1 columns (4.6 mm × 250 mm).

Catalyst (3 mol%) was added to a mixture of aldehydes (2 eq) and ^{i}PrOH:H_2O (0.5:0.5 mL). The pH was adjusted by NMP to pH 5–5.5. After stirring at ambient temperature for 20 min, nitrostyrene (1 eq) was introduced. The reaction mixture was stirred at the same temperature for 5–72 h and then concentrated with a rotary evaporator under reduced pressure and precipitated by EtOAc. The precipitate was filtrated off to reuse, and the EtOAc layer was concentrated. The residue was purified through column chromatography on silica gel by using ethylacetate–n-hexane (1:3) as eluent to give the corresponding Michael adducts for further analysis.

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