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Review Article

Peptide-Catalysis in Asymmetric Organic Synthesis

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HIGHLIGHTS

- Asymmetric catalysis has an impressive progression in the manufacture of pharmaceuticals.
- Enzymes and natural/synthetic peptides are attractive biocatalysts of the chiral reactions.
- Peptides show unique features compared with other catalysts in asymmetric catalysis.

Keywords:
Enzyme
Organic synthesis
Peptide
Stereo-selectivity

ABSTRACT

Stereo-selectivity is an important feature in the development of the synthesis of biologically active organic compounds. In this process, (bio) catalysts exhibit substrate specificity that allows high levels of chemo- and regio-selectivity. Over the past decade, several peptides have been developed as effective bio-catalysts for a range of synthetically valuable reactions. In comparison with proteins owing a large number of amino acids and high molecular weights, peptide-catalysts possess only a few amino acid residues, which may adopt a secondary structure suitable for synthesis of desired chiral products. In addition, the flexible nature of peptides consents for tuning of reactivity and selectivity by replacing amino acid residues. These unique aspects provide attractive biocatalysts platform for asymmetric syntheses.

Introduction

Asymmetric catalysis has effectively changed the procedures of chemical synthesis and has resulted in an impressive progression that raises enormous economic potentials in the manufacture of pharmaceuticals and other biologically active compounds (Cakmak et al., 2016; newton et al., 2016; Das et al., 2017). Catalytic enantio-selective organic reactions can be achieved by either conventional catalysts (mostly metal catalysts) or biocatalysts which offer attractive advantages as an important alternative for traditional chemical catalysts including their availability from renewable resources, biodegradability, mild reaction conditions, and selectivity in both substrate and product stereo-chemistry (Mogharabi et al., 2014). Biocatalysts such as enzymes and natural or synthetic peptides have the potential to perform most of the reactions required for the production of chiral pure and complex molecules with attractive properties (Wachtmeister and Rother, 2017). Enzymes are able to catalyze a broad range of transformations relevant to organic chemistry and asymmetric synthesis that represents a remarkable opportunity for the development of industrial chemical and pharmaceutical processes by various reactions such as redox, bond forming, and hydrolytic reactions (Forootanfar et al., 2011; Rezaei et al., 2017). Enzymes have evolved to work in the cellular environment and suffer serious disadvantage of losing activity in the presence of organic solvents, extremes of pH, and high temperatures. Hence, the development of peptide catalysts with higher stability increases the adoption of biocatalysts in organic synthesis with asymmetric methods.

Based on the wide structural and functional variety

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of peptides that is easily accessible by linking amino acids with different functional groups in their side chains, they possess various essential roles in nature and human life such as hormones, neurotransmitters, toxins, artificial sweeteners, anti-wrinkle additives in creams, and pharmaceuticals (Kenneth et al., 2016). Although peptides are well-known because of their potential biological applications, employing synthetic and natural peptides composed of 2−50 amino acids has flourished over the past decade as effective catalysts in organic synthesis (Table 1). The structural diversity available with short peptide sequences makes this class of remarkable molecules particularly promising for the development of a broad spectrum of small peptide as asymmetric catalysts that mimic various functions of enzymes (Behrendt et al., 2016). In addition, the structural simplicity of the short peptides compared with the complexity of the enzymes provides the easier mechanistic investigations. Over the past decade, several peptides have been developed as effective asymmetric catalysts for a range of synthetically useful organic reactions and the field of asymmetric catalysis with peptides has been established as a promising area at the interface of asymmetric catalysis, peptide chemistry, and enzyme research (Grünenfelder et al., 2016; Procházková et al., 2016; Ueda et al., 2016). Peptides show unique features compared with other small synthetic catalysts and enzymes in asymmetric catalysis of acylation reactions, oxidations, hydrolytic reactions, and carbon-carbon bond formations (Metrano and Miller, 2014; Lio et al., 2016).

Although some studies show that peptide-catalyzed organic reactions have often unique features compared to other small synthetic catalysts and enzymes, one of the major challenges in the development of such biocatalysts is their rational design (Pattabiraman and Bode, 2011). Limited understanding of the necessary requirements of an efficient asymmetric catalyst combined with the difficulty of predicting the conformation of even a simple di- or tri-peptide is still a significant challenge on the rational design of peptides for asymmetric catalysis (Miranda and Alewood, 2000; Han and Kim, 2004; Kent, 2009).

This article represents examples of the recent peptide-catalyzed reactions and highlights their unique features for future applications. Challenges such as the rational design of peptides are also discussed.

Peptide-catalyzed organic reactions

The employment of short peptides as biocatalysts in organic reactions and asymmetric synthesis is a considerable current interest of organic synthesis which comes from the main advantages of small peptide catalysts comparing with other biocatalysts such as structural simplicity, easier mechanistic investigations, and possibility to vary the nature of amino acids to improve the catalyst efficiency. The structural diversity available with short peptide sequences is promising for the development of a broad spectrum of small peptide catalysts that may mimic enzymes. In addition, it is easy to prepare the peptide sequence that can produce the opposite enantiomer. Some representative examples are provided for various peptide-catalyzed organic reactions including epoxidation, oxidation, hydrolysis, acylation, aldol reaction, Michael addition, bromination, and site-selective reactions.

Epoxidation

One of the most well-known enantio-selective, helical chiral peptide-catalyzed oxidation reactions is the asymmetric Weitz-Scheffer asymmetric epoxidation of chalcones, originally developed by Julia´ and Colonna (1980) in the early 1980s. This process has drawn considerable attentions because of the high enantio-selectivity and easily accessible catalysts. As shown in Scheme 1, when (E)-chalcone was treated with aqueous sodium hydroxide and hydrogen peroxide in the presence of the solid poly-L-alanine, underwent epoxidation with a very high degree of enantio-selectivity and provided desired product with up to 96% ee in 24−48 h. Some of the reaction parameters were explored in the epoxidation of (E)-chalcone using peptide catalyst including organic solvent, temperature, and oxidizing agent. Although toluene and tetrachloromethane were the most suitable organic solvents in terms of rate and enantio-selectivity, application of chlorobenzene or dichloromethane decreased the reaction rate but maintained good enantio-selectivity. Less polar solvents such as hexane and cyclohexane provided desired product in an excellent yield but significantly reduced enantiomeric excess. In addition, it was found that when the reaction was run above ambient temperature the enantio-selectivity decreased (Julia´ and Colonna, 1980). The remarkable enantio-selectivity of the Julia´-Colonna epoxidation prompted a number of researchers to conduct further investigations and many studies addressed some of the main disadvantages to the original procedure such as catalyst preparation, catalyst degradation and recovery, and limited substrate scope.

The most effective enantio-selective poly-(amino acid) catalysts are those that adopt R-helical structures. Several investigations have been carried out to further understand the mechanism of asymmetric induction in the Julia´-Colonna epoxidation. A number of approaches have been performed including the synthesis and application of catalysts with varying length, structure, and solubility as well as the use of spectroscopic and computational methods. Early mechanistic studies by Roberts et al. (1997) developed the synthesis of poly-leucine catalysts containing varying amounts of D-leucine. The obtained results showed that the residues at the N-terminus

Table 1. Synthetic peptides used in the asymmetric synthesis of organic compounds.

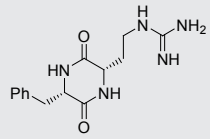
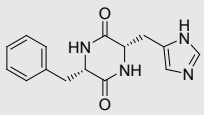
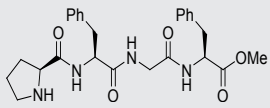
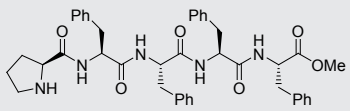
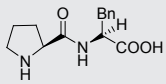
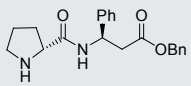
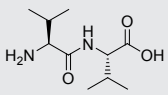
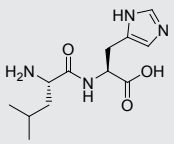
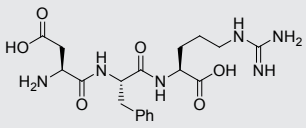
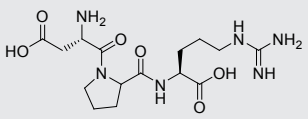
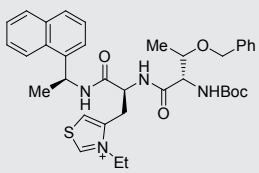
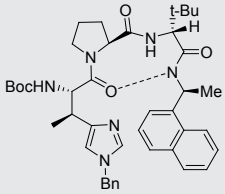
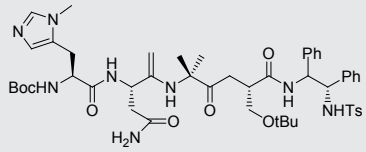
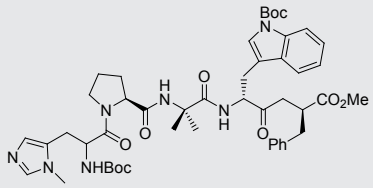
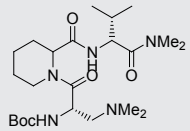
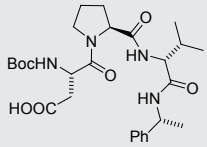
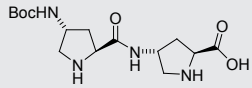
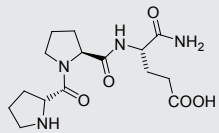
Peptide	Type of reaction	Yield (%)	ee (%)	Reference
	Strecker reaction	97	99	Lipton et al., 1996
	Hydrocyanation	97	97	Asada et al., 1985; Kobayashi et al., 1986
	Aldol reactions	83	91	Tang et al., 2004
	Aldol reactions	76	87	Notz et al., 2000
	Aldol reactions	90	99	Shi et al., 2004
	Aldol reactions	92	74	Luppi et al., 2009
	Aldol reactions	60	68	Cordova et al., 2006
	Michael addition	62	61	Tsogoeva & Jagtap, 2004
	Michael addition	80	77	Tsogoeva et al., 2004
	Michael addition	73	23	Tsogoeva et al., 2004
	Stetter cyclization	67	73	Mennen et al., 2005
	Addition of azide	97	63	Horstmann et al., 2000

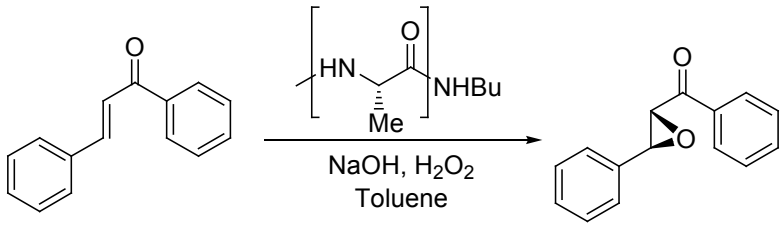
Table 1. (Continued).

Peptide	Type of reaction	Yield (%)	ee (%)	Reference
	Acylation reaction	80	95	Lewis et al., 2008
	Site selective reaction	80	85	Lewis & Miller, 2000
	Bromination	65	74	Gustafson et al., 2010
	Epoxidation	76	83	Jakobsche et al., 2008
	Addition	40	61	Tsogoeva et al., 2006
	Aldol reaction	90	90	Wiesner et al., 2008

exhibited the greatest effect on enantio-selectivity, whereas residues toward the middle and C-terminus demonstrated little effect.

Itsuno and co-workers (1990) reported the use of immobilized peptide (cross-linked by aminomethylated polystyrene resin) for the asymmetric epoxidation of enones. The catalysts were evaluated for efficacy in the enantio-selective epoxidation and it was found that the immobilized poly-L-leucine was an excellent promoter of the reaction, providing product in 92% yield and 99% ee (Itsuno et al., 1990). Such epoxidations were reported in lipase-catalyzed enzymatic reaction. For example, Orellana-Coca et al. (2005) investigated the effect of reaction parameters on lipase-mediated chemo-enzymatic epoxidation of linoleic acid. It was evident that hydrogen peroxide was the most critical parameter influencing the chemo-enzymatic epoxidation reaction and increased in concentration of hydrogen peroxide had a strong positive effect on the reaction kinetics. However, an optimal combination of temperature and concentration of hydrogen peroxide was necessary to achieve complete epoxidation under solvent-free conditions (Coca et al., 2005). Lipase from Candida antarctica conjugated with Pluronic polymers was used for the chemo-enzymatic epoxidation of fatty acids conducted in organic media. The effects of operation parameters including the type of Pluronic polymers and solvents on the epoxidation of different plant oil substrates were examined and it was found that Pluronic F127 and toluene were the best polymer and solvent, respectively. At optimized conditions, a yield of 97%, 75%, and 67% was obtained for epoxidized oleic acid, linoleic acid, and linolenic acid, respectively, using Pluronic F127 conjugated lipase (Yuki et al., 2016).

Peptides-catalyzed epoxidation are comparable with the similar reactions by lipolytic enzymes. Although, the presence of an oxidant such as hydrogen peroxide is necessary for both enzyme- and peptide-catalyzed epoxidation reactions, the structure and activity of enzymes are more influenced than



Scheme 1. Poly-L-alanine-catalyzed epoxidation reaction.

peptides by oxidants and organic solvents.

Oxidation of secondary alcohols

Peptide-catalysts have also been employed in asymmetric alcohol oxidations. Specifically, the kinetic resolution of secondary alcohols has been achieved by the use of nitroxyl-containing peptide catalysts. Formaggio et al. (2002) demonstrated that a non-natural amino acid,2,2,6,6-tetramethylpiperidine-1-oxyl-4-amino-4-carboxylic acid, could be embedded within a peptide and could be effectively served as an oxidizing agent in the presence of alcohols and a sodium hypochlorite solution. Although the mentioned peptide is achiral, it creates a chiral environment around this residue through its secondary structure (Formaggio et al., 2002). On the other hand, laccases which are copper containing oxidoreductase are able to catalyze the oxidation of secondary alcohols in the presence of catalytic amount of 2,2,6,6-tetramethylpiperidine-1-oxyl as a mediator and as the oxidizing agent using molecular oxygen (Mogharabi and Faramarzi, 2014). While the peptide-catalyzed oxidation of secondary alcohols profit from enantio-selectivity obtained from secondary structure of a linked peptide, laccase-catalyzed oxidations are environmental friendly processes which use O_2 as the oxidizing agent in aqueous reaction media.

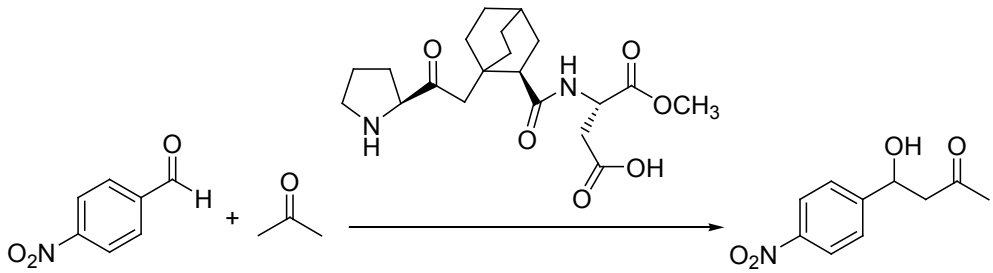
Peptide-catalyzed hydrolysis and acylation

Secondary structure of enzymes and the interaction between active sites and substrates provide efficient reactivity and selectivity in enzyme-catalyzed reactions. Increasing attention has been focused on the development of smaller catalysts that mimic enzymatic mechanisms to increase efficiency and selectivity toward a variety of substrates. Several studies have been performed since the 1970s in order to develop stereo-selective hydrolyses of enantiomeric esters and to understand the mechanism of stereo-selectivity in enzymes. Some efforts were focused on the catalytic system of dipeptide- or tripeptide-type nucleophiles in the presence of surfactants (Matsumoto et al., 1993; Ueoka et al., 1996). Ueoka and colleagues (1999) reported highly diastereo-selective hydrolytic processes of dipeptide esters in a buffered solution without the use of surfactants. In the hydrolysis of peptide esters, diastereo-selectivity could be regulated by controlling temperature, substrate concentration, and pH of the reaction medium.

Acylation can be the reverse process of hydrolysis and nature provides several examples of enzymatic acyl transfer with high efficiency and specificity such as enzymatic acylation of flavonoids, starch, and cellulose (Chebil et al., 2006) Design and development of small molecules for efficient asymmetric acylation have always been a challenge and some representative catalysts reported for asymmetric acylations include phosphine catalysts, chiral pyridine derivatives, other N-heterocycles, and peptide-based catalysts. Miller et al. (1998) applied nucleophilic moiety-embedded peptide structures to find low molecular-weight catalysts for asymmetric acyl transfer reactions. Histidine analogues were chosen to serve as nucleophiles in a series of β-turn type small peptides for the kinetic resolution of trans-1,2-acetamidocyclohexanol. The amide functionality within substrate was designed to introduce potential hydrogen-bonding interactions with the peptide catalyst. The control catalyst, with only one chiral center, showed no selectivity, because of the lack of secondary structure. Catalysts with different stereochemistry on the proline residue (L- or D-) in the peptide backbone exhibited various conformations and reactivates. The presence of D-proline moiety adopted a β-hairpin conformation with two intramolecular hydrogen bonds and it was found that the rigidity of the β-hairpin structure greatly influenced the enantio-selectivity. However, the obtained results from mechanistic investigations showed the importance of the peptide structure of catalyst and the multipoint interactions such as hydrogen bonding, ionic interactions, π-π stacking, and hydrophobic interactions between catalyst and substrate in the peptide-catalyzed asymmetric synthesis.

Aldol reaction

The aldol reaction as a powerful methodology has been



Scheme 2. Aldol reaction between nitrobenzaldehyde and acetone catalyzed by short peptide.

applied to synthesis of many of products by combining either an aldehyde or a ketone and an enolate to yield a α-hydroxycarbonyl compound. Asymmetric aldol reaction provides chiral β-hydroxy carbonyl units which is often included in complex natural or synthetic compounds and constitutes one of the most important and useful carbon-carbon bond-forming reactions. Recently, a series of N-pyrrolidine-based α,β-peptide catalysts were synthesized and evaluated in the asymmetric aldol reaction from acetone and some p-substituted benzaldehydes (Milbeo et al., 2016). Their catalytic properties were shown to be highly dependent on the amino acid sequences and on the absolute configuration of 2-aminobicyclo[2.2.2]octane carboxylic acid residue that played a determinant role. The obtained results showed that among the tested peptides, the heterochiral tripeptide H-Pro-(R)-ABOC-Asp-OCH_3, that adopted a turn conformation in the solid state, proved to be the most efficient catalyst affording β-hydroxy ketones in high yields and enantio-selectivity (Scheme 2).

Michael addition reaction

Akagawa et al. (2016) reported the screening of peptide libraries with N-terminal l- or D-proline under aqueous conditions to obtain capable catalysts for the asymmetric Michael addition of a malonate. From a D-prolyl peptide library, a consensus sequence, D-Pro-D-Pro-X-Trp-X3 was investigated and it was found that the peptide containing lysine in this framework showed good reactivity and enantio-selectivity. In addition, the presence of the tryptophan residue at the fourth position was essential and replacing it with a pyrenylalanine residue improved the catalytic ability (Akagawa et al., 2016). Wiesner et al. (2008) designed a tri-peptide and applied it in asymmetric Michael addition of aldehydes to nitroolefins. A wide range of aliphatic aldehydes was converted with both aliphatic and aromatic nitroalkenes to desired products in 81–99% ee. It was found that the configuration of the amino-terminal proline dictated the stereochemistry of final product and the diastereomer catalyst produced the opposite configuration in the Michael adduct. However, the N-terminal proline environment is responsible for the enamine activation and acceptor is facing donor in a chiral moiety, which is influenced effectively by the configuration at the N-terminus (Scheme 3).

Ueda et al. (2016) reported helical peptide-catalyzed Michael addition reactions of nitroalkane or dialkyl malonate with α,β-unsaturated ketones. The helical peptide was able to catalyze the reaction of a wide variety of α,β-unsaturated ketones including β-aryl, β-alkyl enones, and cyclic enones to give desired products with up to 99% enantio-selectivities. Based on an X-ray crystallographic analysis, the amide protons at the N-terminus in the α-helical peptide catalyst were essential for activating Michael donors, while the Michael acceptors were activated by N-terminal primary amine through the formation of iminium ion intermediates.

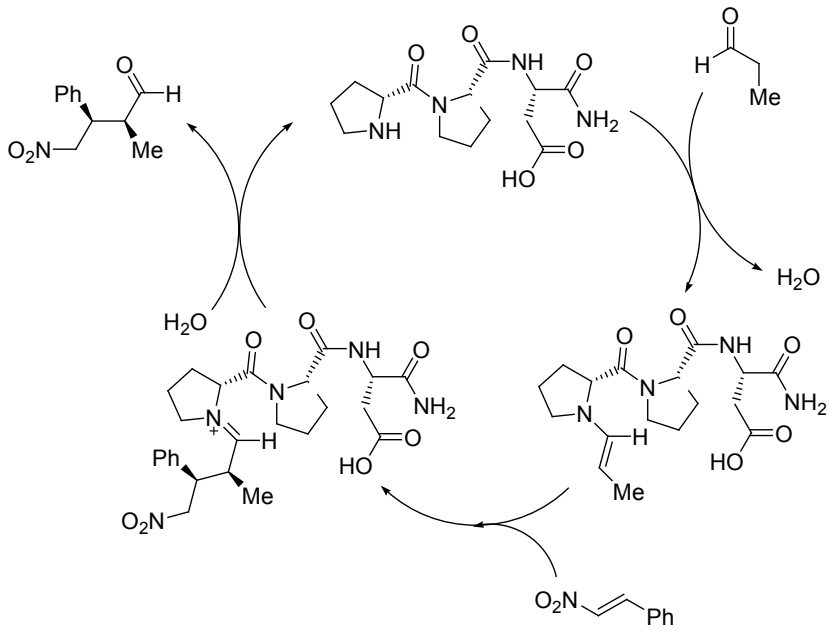
Bromination

Atropisomerism, stereoisomers resulting from hindered rotation about single bond, is an important issue in medicinal chemistry and chiral compounds that exist as separate atropisomers presenting advantages in racemization during selective binding to targeted biological receptors. Diener et al. (2015) reported the development of a tertiary amine-containing β-turn peptide that catalyzed the atroposelective bromination of pharmaceutically relevant 3-arylquinazolin-4(3H)-ones with high levels of enantio-selectivity over a broad substrate scope (Scheme 4).

The catalyst was found to be effective and the unique conformational properties such as barriers to atropisomerization of the products enable site-selective debromination and cross-coupling reactions. In addition, mechanism-driven experiments have also revealed a number of interesting features of these asymmetric reactions, including the likely site of the initial and stereo-determining bromination (Diener et al., 2015).

Site-selective reactions

Site-selective bond formation at redundantly occurring

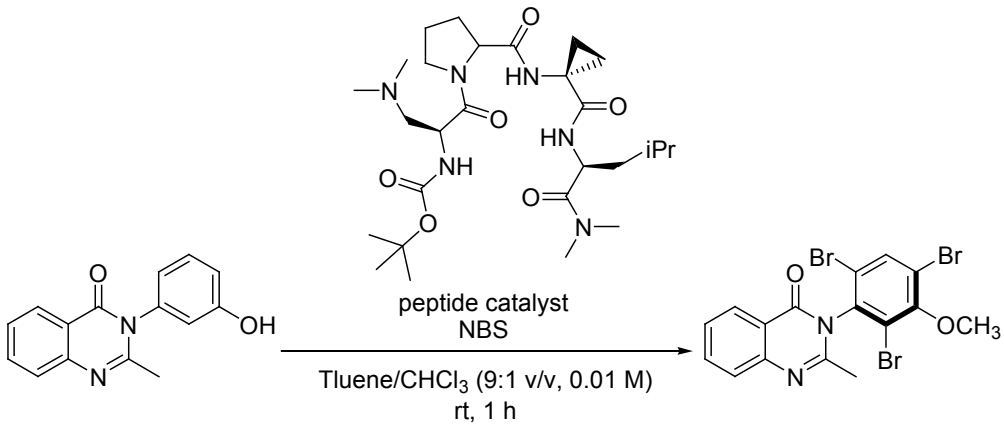


Scheme 3. Proposed mechanism for asymmetric Michael addition of aldehydes to nitroolefins.

functional groups within complex molecules is very difficult. Moreover, particular challenges may exist as the sites become more localized and when the stereochemical relationship is not enantiotopic. Catalysts that target large molecules may not exhibit high preferences for one specific sector of a structure, which may raise the struggle of functionalizing an intrinsically less reactive site in the presence of competing more reactive sites (Lewis and Miller, 2006). However, Han and Miller (2013) investigated three distinct, peptide-based catalysts that enabled site-selective phosphorylation of three distinct hydroxyl groups within three distinct sugar moieties presented in teicoplanin A2-2 (Scheme 5). Rational design of catalysts based on the X-ray crystal structure and modeling enabled the identification of peptide which selectively phosphorylated the N-decanoylglucosamine moiety. Notably, these catalysts are considerably smaller than the substrate and it is a unique situation among many classes of catalysts similar to real enzymes (Han and Miller 2013). Acyl transfer reaction is known as one of the most important chemical reactions occurring in biological systems as well as in organic synthesis, where it is widely used in enantio-selective catalysis. Procházková et al. (2016) reported a highly enantio-selective oligopeptide catalyst that was used for the kinetic resolution of trans-cycloalkane-1,2-diols via monoacylation (Scheme 6). Potentially useful goal in the synthesis of polyfunctional molecules could be achieved by applying site-selective functionalization of polyfunctional substrates. Although enzymes demonstrate high efficiency and selectivity in such processes, their very limited substrate scope restricts each possible enzymatic model. Therefore, the structure of a small peptide catalyst can be easily manipulated, and the efficient synthesis of a small peptide library makes it a possibly practical tool in regio-selective functionalization of polyfunctional substrates reactions.

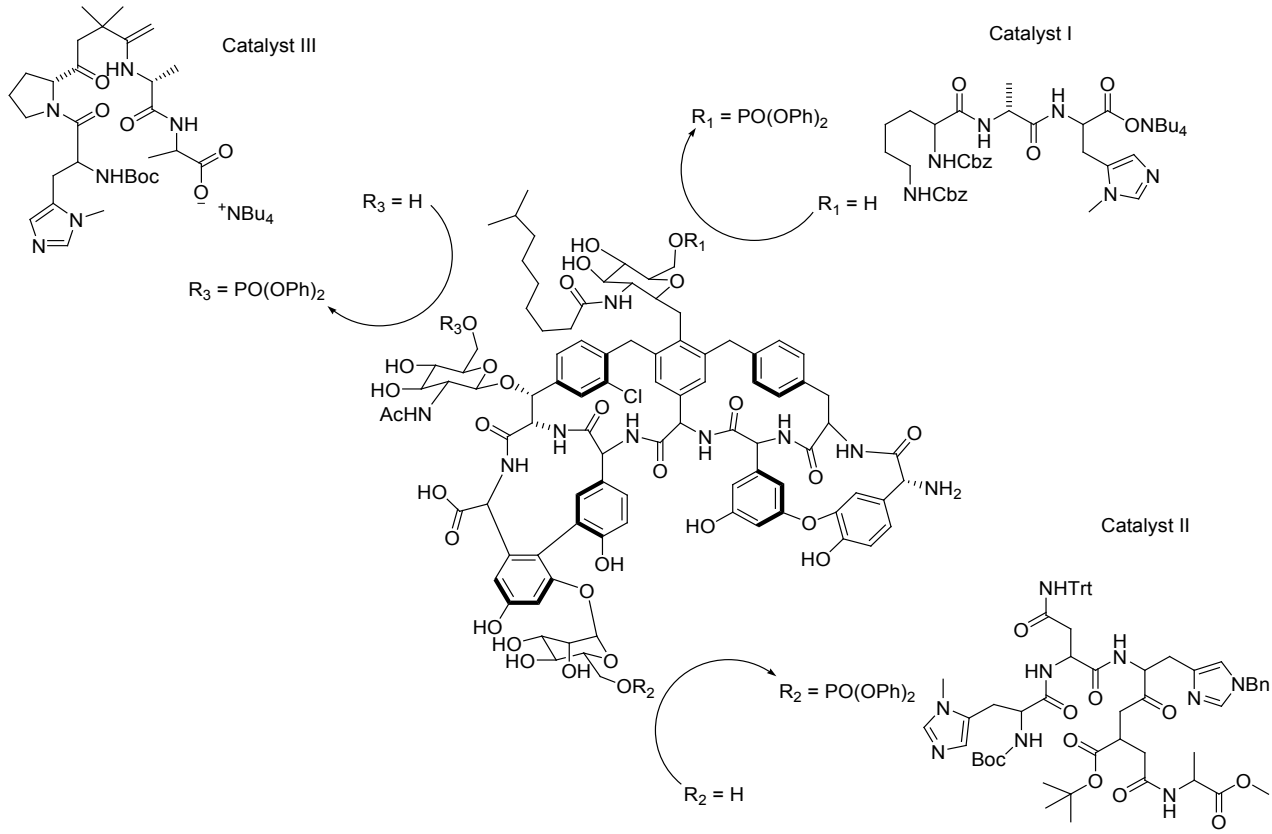
Rational design of catalytic peptide

One of the major challenges in the development of peptide catalysts is their rational design. Limited understanding of the necessary requirements of an efficient asymmetric catalyst combined with the difficulty of predicting the conformation of even a simple di- or tri-peptides is still posing an important challenge on the rational design of peptide catalysts. Using combinatorial chemistry has played a key role in establishing effective asymmetric peptide catalysts. In particular, the testing of libraries as a tool that allows for the generation of a large degree of molecular diversity and also with colorimetric or fluorescence based screening methods allowed for the identification of several effective peptide catalysts (Wennemers, 2011).Basically, the peptide formation goes through a repetitive amide formation reaction between an amino group of one amino acid and the carboxylic group of a second one. Fischer & fourneau (1901) demonstrated that amino acids were the building blocks of proteins and synthesized the first synthetic peptide (glycyl–

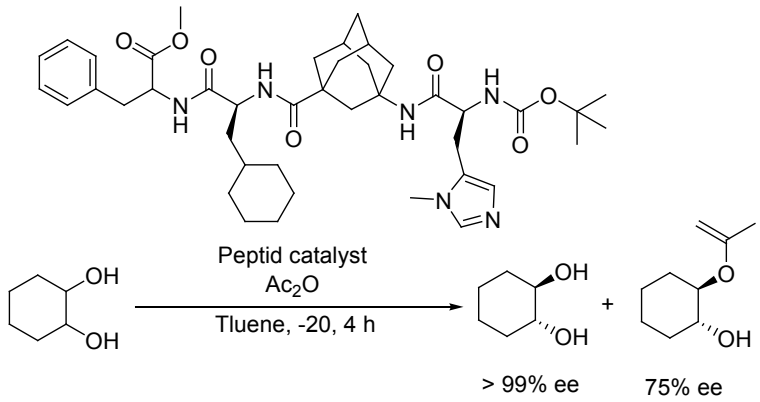


Scheme 4. Enantio-selective synthesis of 3-arylquinazolin-4(3H)-ones via peptide-catalyzed atroposelective bromination.

glycine) by hydrolysis of the glycine diketopiperazine. For the first time, Bruce Merrifieldeld in 1963 reported generating peptide bonds on an insoluble resin where a single cleavage step permitted obtaining the desired peptide in solution. In solid-phase peptide synthesis, the peptide chain was assembled in a stepwise method while the C-terminal of the peptide was attached to an inert cross-linked polymer support and the peptide was grown



Scheme 5. Site-selective phosphorylation of three distinct hydroxyl groups within the complex glycopeptide antibiotic teicoplanin.



Scheme 6. Enantio-selective peptide-catalyzed acylation of cyclohexane-1, 2-diol.

from C-terminal to N-terminal residue (Palomo, 2014). Coupling specific pairs of amino acids in precise order is very complicated because of reactive α-carboxylic acids, α-amine groups, and reactive side chain functional groups of amino acids. Chemical groups have been developed to facilitate the synthesis of peptides with precise amino acid sequences with blocking all functional groups present in amino acids except that desired pair. The two most widely used are the tert-butoxycarbonyl group (sensitive to acids such as trifluoroacetic acid), and the fluoren-9-ylmethyloxycarbonyl group (sensitive to bases such as piperidine) (Behrendt et al., 2016).

Conclusion

Over the past decade, the ability of peptides to catalyze a wide range of various organic reactions is complimented by their availability, stability, and ease of handling. Peptides composed of chiral amino acids with stable secondary and tertiary structures provide asymmetric environment leading to efficiently control of selective formation of enantiomerically pure product. Using peptides alongside the large and folded proteins has emerged as an efficient catalyst that can promote a number of stereo-selective chemical reactions and serve an exciting prologue for continuous developments of asymmetric organic reactions in future.

Competing Interests

The authors declared that there are no competing interests.

References

Akagawa, K., Iwasaki, Y. and K. Kudo, (2016). "Library screening in aqueous media to develop a highly active peptide catalyst for enantioselective Michael addition of a malonate." *European Journal of Organic Chemistry*, **2016**(26): 4460–4464.

Behrendt, R., White, P. and J. Offer, (2016). "Advances in Fmoc solid-phase peptide synthesis." *Journal of Peptide Science*, **22**(1): 4–27.

Cakmak, Y., Erbas-Cakmak, S. and D. A. Leigh, (2016). "Asymmetric catalysis with a mechanically point-chiral rotaxane." *Journal of the American Chemical Society*, **138**(6): 1749–1751.

Chebil, L., Humeau, C., Falcimaigne, A., Engasser, J. M. and M. Ghoul, (2006). "Enzymatic acylation of flavonoids." *Process Biochemistry*, **41**(11): 2237–2251.

Das, S., Majumdar, N., De, C. K., Kundu, D. S., Döhring, A., Garczynski, A. and B. List, (2017). "Asymmetric catalysis of the carbonyl-amine condensation: kinetic resolution of primary amines." *Journal of the American Chemical Society*, **139**: 1357-1359.

Diener, M. E., Metrano, A. J., Kusano, S. and S. J. Miller, (2015). "Enantioselective synthesis of 3-arylquinazolin-4 (3 H)-ones via peptide-catalyzed atroposelective bromination." *Journal of the American Chemical Society*, **137**(38): 12369–12377.

Fischer, E. and E. Fourneau, (1901). "Ueber einige derivate des glykocolls." *European Journal of Inorganic Chemistry*, **34** (2): 2868–2877.

Formaggio, F., Bonchio, M., Crisma, M., Peggion, C., Mezzato, S., Polese, A., Barazza, A., Antonello, S., Maran, F., Broxterman, Q.B. and B. Kaptein, (2002). "Nitroxyl peptides as catalysts of enantioselective oxidations." *Chemistry–A European Journal*, **8**(1): 84–93.

Forootanfar, H., Faramarzi, M. A., Shahverdi, A. R. and M. T. Yazdi, (2011). "Purification and biochemical characterization of extracellular laccase from the ascomycete *Paraconiothyrium variabile*." *Bioresource Technology*, **102**(2): 1808–1814.

Grünenfelder, C. E., Kisunzu, J. K. and H. Wennemers, (2016). "Peptide-catalyzed stereoselective conjugate addition reactions of aldehydes to maleimide." *Angewandte Chemie International Edition*, **55**(30): 8571–8574.

Gustafson, J. L., Lim, D. and S. J. Miller, (2010). "Dynamic kinetic resolution of biaryl atropisomers via peptide-catalyzed asymmetric bromination." *Science*, **328**(5983): 1251–1255.

Han, S. Y. and Y. A. Kim, (2004). "Recent development of peptide coupling reagents in organic synthesis." *Tetrahedron*, **60**(11): 2447–2467.

Han, S. and S. J. Miller, (2013). "Asymmetric catalysis at a distance: catalytic, site-selective phosphorylation of teicoplanin." *Journal of the American Chemical Society*, **135** (33): 12414–12421.

Horstmann, T. E., Guerin, D. J. and S. J. Miller, (2000). "Asymmetric

Conjugate Addition of Azide to α, β-Unsaturated Carbonyl Compounds Catalyzed by Simple Peptides." *Angewandte Chemie*, **112**(20): 3781–3784.

Itsuno, S., Sakakura, M. and K. Ito, (1990). "Polymer-supported poly (amino acids) as new asymmetric epoxidation catalyst of. alpha.,.beta.-unsaturated ketones." *The Journal of Organic Chemistry*, **55**(24): 6047–6049.

Jakobsche, C. E., Peris, G. and S. J. Miller, (2008). "Functional Analysis of an Aspartate-Based Epoxidation Catalyst with Amide-to-Alkene Peptidomimetic Catalyst Analogues." *Angewandte Chemie International Edition*, **47**(35): 6707–6711.

Juliá, S., Masana, J. and J. C. Vega, (1980). "Synthetic Enzymes". Highly Stereoselective Epoxidation of Chalcone in a Triphasic Toluene-Water-Poly [(S)-alanine] System." *Angewandte Chemie International Edition in English*, **19**(11): 929–931.

Kent, S. B. (2009). "Total chemical synthesis of proteins." *Chemical Society Reviews*, **38**(2): 338–351.

Lewis, C. A. and S. J. Miller, (2006). "Site-selective derivatization and remodeling of erythromycin A by using simple peptide-based chiral catalysts." *Angewandte Chemie*, **118**(34): 5744–5747.

Lewis, C. A., Gustafson, J. L., Chiu, A., Balsells, J., Pollard, D., Murry, J. and S. J. Miller, (2008). "A case of remote asymmetric induction in the peptide-catalyzed desymmetrization of a bis (phenol)." *Journal of the American Chemical Society*, **130**(48): 16358–16365.

Liao, R. Z., Santoro, S., Gotsev, M., Marcelli, T. and F. Himo, (2016). "Origins of stereoselectivity in peptide-catalyzed kinetic resolution of alcohols." *ACS Catalysis*, **6**(2): 1165–1171.

Mennen, S. M., Blank, J. T., Tran-Dubé, M. B., Imbriglio, J. E. and S. J. Miller, (2005). "A peptide-catalyzed asymmetric Stetter reaction." *Chemical Communications*, **2**: 195–197.

Metrano, A. J. and S. J. Miller, (2014). "Peptide-catalyzed conversion of racemic oxazol-5 (4 H)-ones into enantiomerically enriched α-amino acid derivatives." *The Journal of Organic Chemistry*, **79**(4): 1542–1554.

Milbeo, P., Maurent, K., Moulat, L., Lebrun, A., Didierjean, C., Aubert, E., Martines, J. and M. Calmes, (2016). "N-Pyrrolidine-based α/β-peptides incorporating ABOC, a constrained bicyclic β-amino acid, for asymmetric aldol reaction catalysis." *Tetrahedron*, **72**(13): 1706–1715.

Miranda, L. P. and P. F. Alewood, (2000). "Challenges for protein chemical synthesis in the 21st century: bridging genomics and proteomics." *Peptide Science*, **55**(3): 217–226.

Mogharabi, M. and M. A. Faramarzi, (2014). "Laccase and laccase-mediated systems in the synthesis of organic compounds." *Advanced Synthesis & Catalysis*, **356**(5): 897–927.

Matsumoto, Y., Matsumoto, Y., Inoue, J. and R. Ueoka, (1993). "Extraordinary diastereoselectivity coupled to altered structure of dipeptide esters." *Chemistry Letters*, **22**(8): 1303–1304.

Newton, C. G., Kossler, D. and N. Cramer, (2016). "Asymmetric catalysis powered by chiral cyclopentadienyl ligands." *Journal of the American Chemical Society*, **138**(12): 3935–3941.

Orellana-Coca, C., Camocho, S., Adlercreutz, D., Mattiasson, B., and R. Hatti-Kaul, (2005). "Chemo-enzymatic epoxidation of linoleic acid: Parameters influencing the reaction." *European Journal of Lipid Science and Technology*, **107**(12): 864–870.

Palomo, J. M. (2014). "Solid-phase peptide synthesis: an overview focused on the preparation of biologically relevant peptides." *RSC Advances*, **4**(62): 32658–32672.

Pattabiraman, V. R. and J. W. Bode, (2011). "Rethinking amide bond synthesis." *Nature*, **480**(7378): 471–479.

Procházková, E., Kolmer, A., Ilgen, J., Schwab, M., Kaltschnee, L., Fredersdorf, M., Schmidts, V., Wende, R. C., Schreiner, P. R. and C. M. Thiele, (2016). "Uncovering key structural features of an enantioselective peptide-catalyzed acylation utilizing advanced NMR techniques." *Angewandte Chemie International Edition*, **55**(51): 15754–15759.

Rezaei, S., Shahverdi, A. R. and M. A. Faramarzi, (2017). "Isolation, one-step affinity purification, and characterization of a polyextremotolerant laccase from the halophilic bacterium *Aquisalibacillus elongatus* and its application in the delignification of sugar beet pulp." *Bioresource Technology*, **230**: 67–75.

Schwieter, K. E. and J. N. Johnston, (2016). "On-demand complex peptide synthesis: an aspirational (and Elusive) goal for peptide synthesis." *Journal of the American Chemical Society*, **138**(43): 14160–14169.

Tsogoeva, S. B. and S. B. Jagtap, (2004). "Dual catalyst control in the chiral diamine-dipeptide-catalyzed asymmetric Michael addition." *Synlett*, **2004**(14): 2624–2626.

Tsogoeva, S. B., Jagtap, S. B., Ardemasova, Z. A. and V. N. Kalikhevich, (2004). "Trends in asymmetric Michael reactions catalysed by tripeptides in combination with an achiral additive in different solvents." *European Journal of Organic Chemistry*, **2004**(19): 4014–4019.

Tsogoeva, S. B., Jagtap, S. B. and Z. A. Ardemasova, (2006). "4-trans-Amino-proline based di-and tetrapeptides as organic catalysts for asymmetric C–C bond formation reactions." *Tetrahedron: Asymmetry*, **17**(6): 989–992.

Ueda, A., Umeno, T., Doi, M., Akagawa, K., Kudo, K. and M. Tanaka, (2016). "Helical-Peptide-catalyzed enantioselective michael addition reactions and their mechanistic insights." *The Journal of Organic Chemistry*, **81**(15): 6343–6356.

Ueoka, R., Matsumoto, Y., Goto, K., Ito, T., Mori, S., Matsumoto, Y., Sakoguchi, A., Ihara, Y. and F. Hirata, (1996). "A remarkably enhanced diastereoselectivity for the hydrolysis of dipeptide esters responding to pH and temperature in buffer solutions." *Tetrahedron Letters*, **37**(20): 3461–3464.

Ueoka, R., Goto, K., Tanoue, O., Miki, A., Yoshimitsu, S., Imamura, C., Ihara, Y. and Y. Murakami, (1999). "Diastereoselective specificity for the hydrolysis of dipeptide esters in aqueous media." *Chemistry Letters*, **28**(1): 73–74.

Wachtmeister, J. and D. Rother, (2016). "Recent advances in whole cell biocatalysis techniques bridging from investigative to industrial scale." *Current Opinion in Biotechnology*, **42**: 169–177.

Wiesner, M., Revell, J. D. and H. Wennemers, (2008). "Tripeptides as Efficient Asymmetric Catalysts for 1,4-Addition Reactions of Aldehydes to Nitroolefins–A Rational Approach." *Angewandte Chemie*, **120**(10): 1897–1900.

Wennemers, H. (2011). "Asymmetric catalysis with peptides." *Chemical Communications*, **47** (44): 12036–12041.

Yuki, O., Zhang, Y., Ge, J. and Z. Liu, (2016). "Epoxidation of Fatty Acids by Pluronic-Conjugated Lipase in Organic Media." *Catalysis Letters*, **146**(6): 1073–1078.