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Asymmetric catalysis with short-chain peptides

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Within this review article we describe recent developments in asymmetric catalysis with peptides. Numerous peptides have been established in the past two decades that catalyze a wide variety of transformations with high stereoselectivities and yields, as well as broad substrate scope. We highlight here catalytically active peptides, which have addressed challenges that had thus far remained elusive in asymmetric catalysis: enantioselective synthesis of atropoisomers and quaternary stereogenic centers, regioselective transformations of polyfunctional substrates, chemoselective transformations, catalysis in-flow and reactions in aqueous environments.

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Introduction

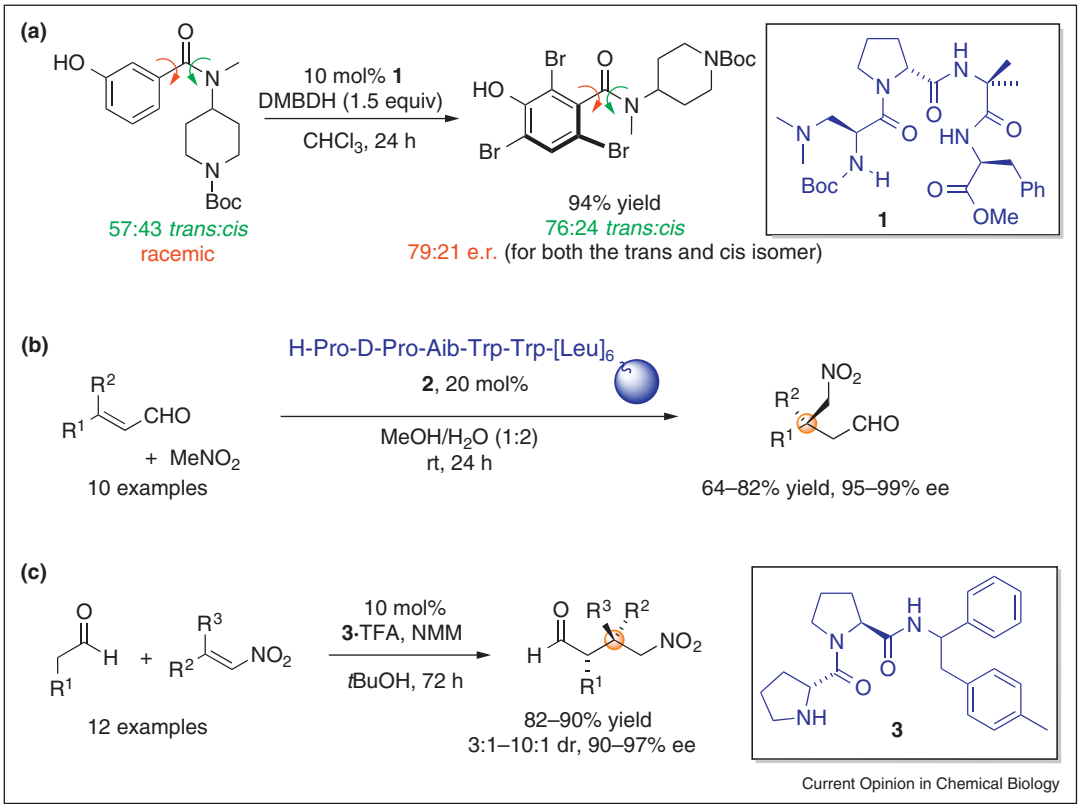
Peptides fulfil a multitude of different functions in nature and everyday life as, hormones, neurotransmitters, toxins, therapeutics against numerous diseases, and artificial sweeteners [1]. Despite this functional versatility, the value of peptides for asymmetric catalysis has only been recognized in the past two decades [2,3]. Apart from early reports on cyclic dipeptides and polyleucines for catalytic asymmetric hydrocyanations [4] and epoxidations [5], respectively, the field remained dormant until the late 1990s. The establishment of numerous effective peptidic catalysts since then, is closely connected to the development of smart combinatorial screening methods that allowed the discovery of lead structures by overcoming the challenge of rationally designing potent catalyst structures [6]. Nowadays, the palette of reactions for which peptidic catalysts are available is broad and includes, for example, stereoselective acylations, phosphorylations, brominations, epoxidations, aldol, and numerous other C–C bond forming reactions [2,3]. Recent advances in the field also revealed that the structural and functional diversity of peptides offers unique opportunities for tackling challenges that are difficult to address by other less modular catalyst structures. These include the development of catalysts for highly challenging enantioselective reactions, regioselective and chemoselective transformations, as well as metal-free catalysis at low catalyst loadings and in continuous flow. Within this report we will showcase these features with a focus on latest highlights that have not been covered in previous reviews [2,3].

Challenging enantioselective reactions

Whereas numerous metalorganic and metal-free catalysts have been developed for enantioselective formations of stereogenic centers, the stereoselective installation of axial chirality has proven to be significantly more difficult. Miller provided a solution to this challenge with a tetrapeptidic catalyst that brominates substituted, tertiary benzamides to yield atropoisomeric tribromo products with excellent enantioselectivities [7]. Using the same tetrapeptide **1** the group also achieved dynamic kinetic resolution of atropoisomers of unsymmetrical tertiary benzamides with two axes of chirality; one defined through the benzamide structure, the other associated with the different substituents on the amide nitrogen (Figure 1a) [8•]. The interplay of kinetic and thermodynamic parameters of the enantioselective bromination and isomerisation of the amide bond led to a product distribution with equal stereochemical enrichment of both the *cis* and *trans* amide isomers. This impressive control over the dynamics of the system not only allowed to obtain the target compound with high stereoselectivity but is also potentially of great value for the design of molecular switches or motors as well as ligands for metal-based asymmetric catalysts [9].

Acyclic compounds containing all-carbon, quaternary stereocenters represent another class of challenging molecules for asymmetric synthesis [10]. Kudo tackled this challenge with the 11-mer helical peptide **2** that catalyzes Michael reactions between nitromethane and β,β-disubstituted aldehydes (Figure 1b) [11•]. Wennemers accessed the same type of γ-nitroaldehydes with two consecutive stereogenic centers by conjugate addition reactions between aliphatic aldehydes and β,β-disubstituted nitroolefins, promoted by the H-d-Pro-Pro based catalyst **3** (Figure 1c) [12••]. Of note, side reactions such as homo-aldol reactions, which had impeded the development of effective catalysts for this conjugate addition reaction, occur in the presence of tripeptide **3** only to a minor extent. This shows the high level of chemoselectivity of **3**. The target γ-nitroaldehydes were obtained in very high yields as well as enantioselectivities and

Figure 1



Enantioselective peptide-catalyzed reactions providing access to structurally challenging molecules: **(a)** dynamic kinetic resolution of atropoisomers of a tertiary benzamide with tetrapeptide catalyst **1**; **(b,c)** conjugate addition reactions providing acyclic γ-nitroaldehydes with all-carbon stereogenic centers.

diastereoselectivities. Their synthetic versatility was additionally demonstrated by conversion to a range of useful, chiral building blocks [12••].

Peptide-catalyzed regioselective reactions

Enzymes typically discriminate near-perfectly not only between different substrates but also different reactive sites within a given substrate. In contrast, traditional synthetic catalysts discriminate poorly between identical functional groups within the same molecule that differ only by their chemical environment [13]. Miller and coworkers showed that peptidic catalysts, while being of significantly lower molecular weight than enzymes, have the right degree of complexity to distinguish between the same type of functional group and favor reactions also at intrinsically less reactive sites. Initial studies showed impressive levels of discrimination by peptidic acylation and phosphorylation catalysts between hydroxyl groups within complex natural products such as erythromycin and teicoplanin [14,15]. Recently, pentapeptide **4** and tripeptide **5** were developed for site-selective thiocarbonylations of vancomycin (Figure 2a) [16•]. Both bear a reactive methyl-imidazole (Me-Imi) group that activates and transfers the thiocarbonyl moiety to the preferred hydroxyl group, which can then be selectively removed. The resulting derivatives are highly valuable for deciphering the mode of action of vancomycin. Whereas peptide **4** thiocarbonylates preferentially the more reactive benzylic alcohol and enhances the intrinsic reactivity to a 9:1 product ratio, peptide **5** reacts preferentially with the less reactive primary hydroxyl group of the sugar moiety and provides the products in a 27:1 ratio. Whereas peptide **4** was the result of screening a small collection of 25 Me-Imi containing peptides, **5** was rationally designed based on the dipeptide motif D-Ala-D-Ala, which is present in bacterial cell walls and binds to vancomycin selectively. The replacement of one D-Ala moiety by D-(Me)His allowed for catalytic turnover, yet, high catalyst loadings of 20 mol% were necessary [16•]. In a related study the group used a D-Ala-D-Ala containing tripeptide for site-selective brominations of vancomycin that yielded previously unknown monobromo-vancomycin, dibromo-vancomycin and a tribromo-vancomycin derivative [17]. However due to the high affinity of D-Ala-D-Ala for both the vancomycin substrate and the product stoichiometric amounts of the peptide were required.