Expedient and Divergent Synthesis of Unnatural Peptides through Cobalt-Catalyzed Diastereoselective Umpolung Hydrogenation

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In recent years, there has been a growing interest in harnessing peptides as therapeutic agents for treating various diseases. Currently, the global market boasts more than 80 commercially available peptide drugs, with approximately 170 in diverse stages of clinical trials and an additional 500 undergoing preclinical studies. Unnatural peptides with amino acid residues beyond the 20 canonical amino acids have demonstrated superior proteolytic stability, bioactivity and pharmacokinetics compared with their natural counterparts. Among them, noncanonical aryl alanines are notably prevalent in pharmaceuticals due to their exceptional versatilities (Figure 1). Consequently, the ongoing exploration of methods to synthesize unnatural peptides containing noncanonical aryl alanine residues and their potential therapeutic applications remains highly desirable.

In a recent publication in *Science Advances*, the group of Professors Xurong Qin and Qiao Ren at Southwest University (P. R. of China) developed a diastereo- and regioselective cobalt-catalyzed umpolung hydrogenation for the divergent and expedient synthesis of unnatural aryl alanine peptides (Scheme 1E). In this research article, they disclosed that commercially available acetic acid and methanol can serve as safe

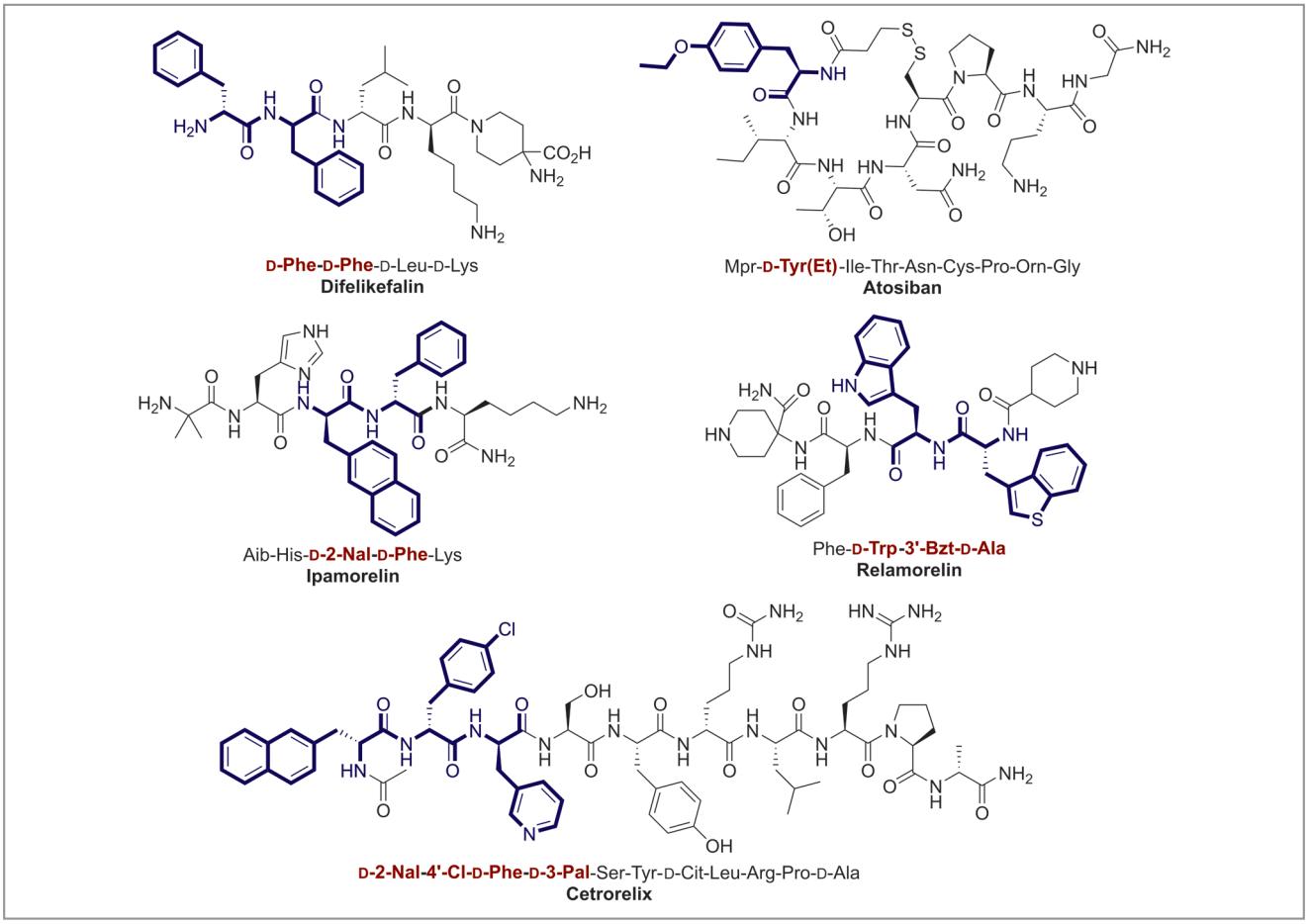

Figure 1 Selected peptide drugs containing unnatural aryl alanine residues

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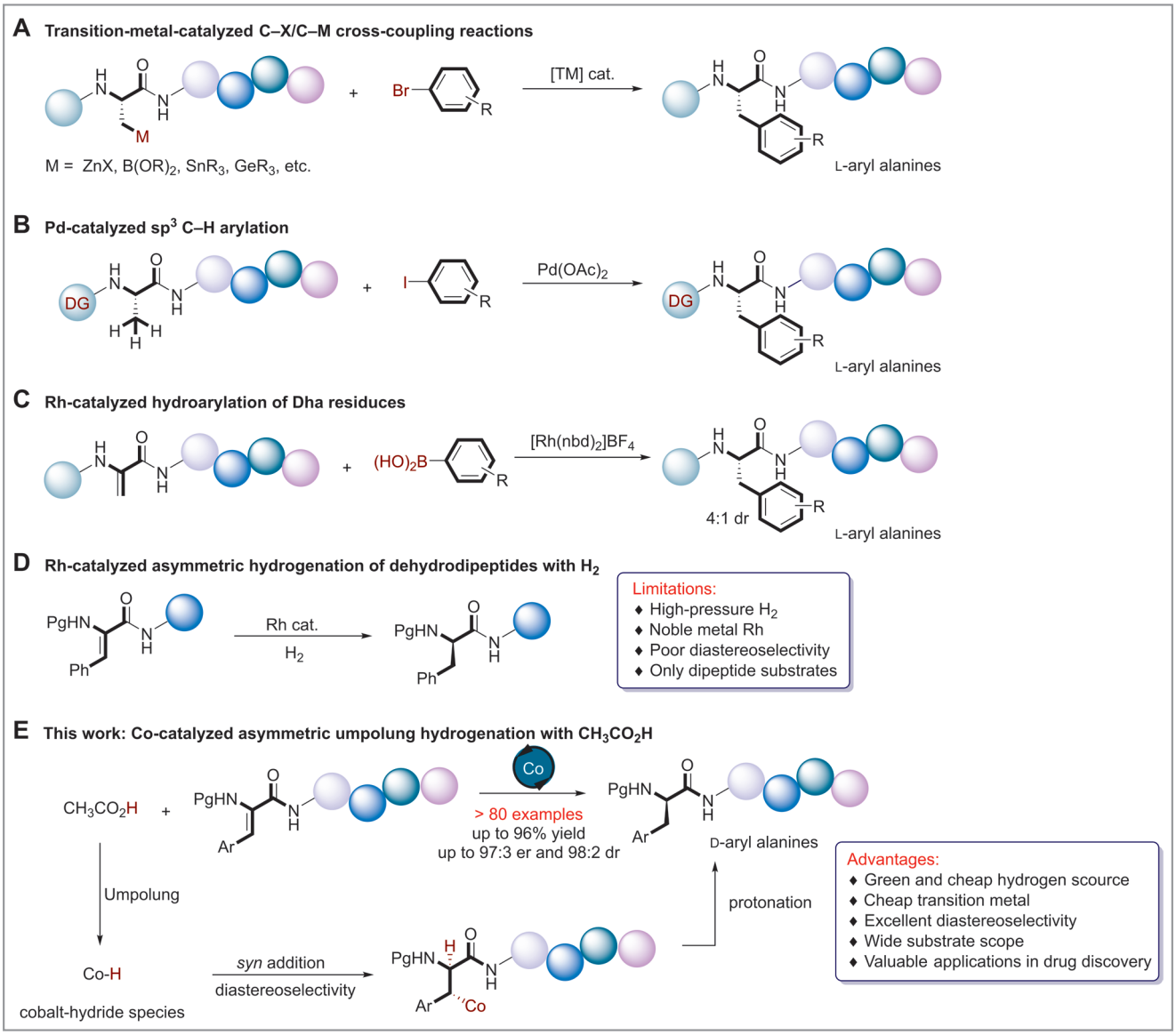
and cheap hydrogen sources, avoiding the safety hazards associated with the storage and usage of high-pressure hydrogen gas.

Professor Qin explained to SYNFORM the background of their work and the research questions they aimed to answer at the onset of the project. "The coupling reagent mediated condensation of unnatural aryl alanines through dehydration is a widely used and reliable approach for peptide formation. However, this approach has several limitations, including the tedious preparation of unnatural aryl alanines, poor atom economy, inevitable side reactions, and the potential risk for racemization/epimerization of the α-stereocenter caused by the over-activation of carboxyl groups by coupling reagents," he said, continuing: "An alternative strategy involves the transition-metal-catalyzed cross-coupling reactions between aryl halides and Ala^{M} reagents (Scheme 1A). While this reaction provides reliable access to L-aryl alanine moieties, it still grapples with limitations, such as the labile or challenging-to-synthesize nature of some Ala^{M} reagents." Recent groundbreaking work by several groups, including Lavilla/Albericio, Ackermann, Yu, Wang, and Chen, has pioneered Pd-catalyzed C–H arylation of L-alanine derivatives to produce unnatural



Scheme 1 Transition-metal-catalyzed methods of unnatural aryl alanine residues incorporation in peptides

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aryl alanine peptides (Scheme 1B). However – according to Professor Qin – this protocol typically demands an external directing group for excellent site-selectivity, leading to additional and cumbersome steps for installation and detachment, sometimes even irremovability. "Another approach is Rh-catalyzed hydroarylation of dehydroalanines, which can provide unnatural aryl alanine peptides in 4:1 dr (Scheme 1C). Although there has been some progress in rhodium-catalyzed hydrogenation of dehydrodipeptides using H_2 gas (at 30–70 atm under specific conditions), significant challenges persist (Scheme 1D). These challenges mainly revolve around limited structural diversity, especially concerning peptide length, and the relatively modest level of diastereoselectivity achieved thus far," he said.

Professor Qin explained further: "Transition-metal-catalyzed asymmetric hydrogenation has been certified as a powerful tool for the preparation of a wide range of pharmaceuticals, agrochemicals, bioactive compounds, and natural products. However, most asymmetric hydrogenation catalysts are based on scarce and costly heavy noble metals including Rh, Ru, Ir, and Pd, occurring at very low abundances in the earth's crust ($5x10^{-5}$–10^{-4} ppm). In addition, these heavy noble metals not only incur high costs in the production process but also require recovery and recycling due to environmental concerns." Recently, according to Professor Qin, there has been a renewed interest in using low-cost, earth-abundant, and biologically compatible 3d transition metal catalysts such as Mn, Fe, Co, Ni, and Cu for asymmetric hydrogenation. However, these strategies might employ high-pressure hydrogen gas, a severe safety hazard during transport, storage and use.

"In our recent work, described in the title article, a wide range of dehydropeptides with varying lengths, sequences, and steric/electronic properties, were successfully hydrogenated into the corresponding unnatural aryl alanine-based peptides in moderate to excellent yields and with high enantioselectivities or diastereoselectivities," said Professor Qin, who continued: "This protocol can also be successfully extended to biologically relevant molecules and pharmaceutically derived dehydropeptides." Notably, the formal synthesis of several representative natural products and drugs further exemplified the versatility of this catalytic hydrogenation system. "Besides," emphasized Professor Qin, "this strategy eliminates the need for synthesizing chiral noncanonical aryl alanines before peptide formation, and this hydrogenation reaction does not result in racemization or epimerization. Importantly, the underlying mechanism was extensively explored through deuterium labeling, control experiments, HRMS identification, and UV-Vis spectroscopy, which supported a reasonable Co^{I}/Co^{III} catalytic cycle."

Professor Qin concluded: "We believe that this cobalt-catalyzed umpolung hydrogenation offers a novel approach for the divergent and efficient synthesis of unnatural aryl alanine peptides using readily available sources. This research holds appeal for both the chemical and medicinal communities."

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