Enantioselective Three-Component Aminomethylation of α-Diazo Ketones with Alcohols and 1,3,5-Triazines

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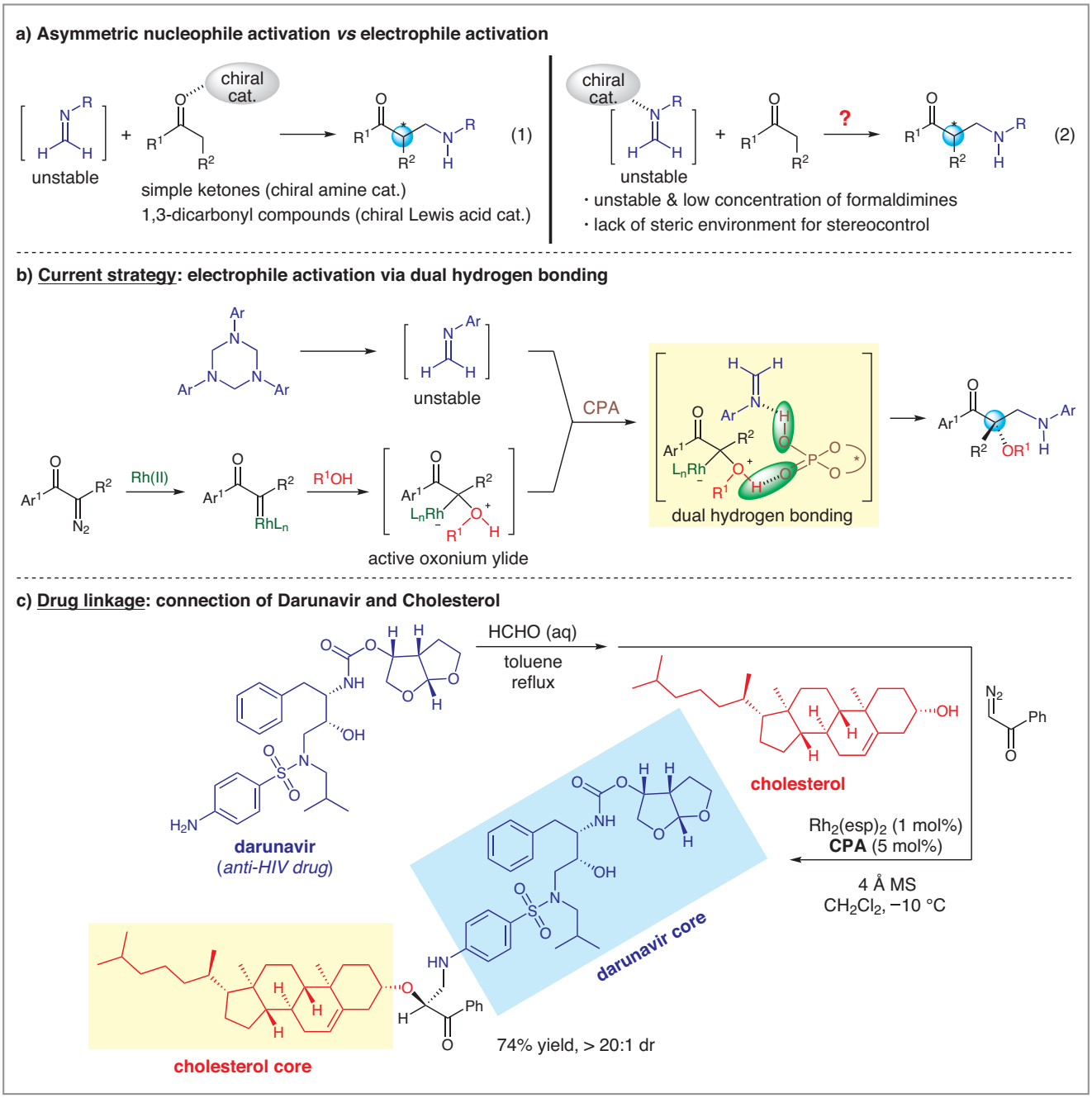
β-Amino carbonyl moieties are versatile synthetic building blocks that can be employed toward a wide variety of natural products and biologically active compounds. As an important research branch of the Mannich reaction, the aminomethylation reaction of ketones or aldehydes represents an efficient protocol for accessing β-amino carbonyl compounds. "Recent years have witnessed the application of a variety of aminomethylation reagents to the enantioselective variant of the reaction; however, asymmetric induction of these transformations is dominated by the use of chiral catalysts to activate the nucleophiles, i.e. chiral amines or Lewis acids with chiral ligands," said Professor Dong Xing from East China Normal University (P. R. of China), adding: "While this nucleophile-based activating strategy was feasible and showed good enantiocontrol, the nucleophiles were limited to inherently activated substrates such as unmodified ketones or 1,3-dicarbonyl compounds, thus the scope and application of this type of transformation were also significantly limited (Scheme 1, a)."

The groups of Professor Xing and Professor Wenhao Hu (Sun Yat-sen University, P. R. of China) have a long-standing common research interest in carbene-involved enantioselective multicomponent reactions (MCRs) via cooperative catalysis. "As part of our ongoing research, we designed the rhodium(II)/chiral phosphoric acid (CPA) co-catalysed three-component reaction of α-diazo ketone, alcohol and 1,3,5-triaryl-1,3,5-triazine, with the hope that an electrophile activation strategy would be established (Scheme 1, b)," said Professor Hu, continuing: "However, due to the instability and low concentration properties of the formaldimine species generated in situ from 1,3,5-triazine, it remains uncertain whether such an electrophile activation mode is workable."

At the very beginning of their exploration, tremendous efforts were made to modify the reaction conditions with different α-carbonyl diazo compounds as the carbene precursor. "It finally turned out that the structure of the diazo compound has a significant impact on the outcome of the reaction," explained Professor Xing. He added: "We continually noticed that the structure of both the CPA and the rhodium(II) catalyst are both responsible for the stereoselective control of this transformation."

With the established optimized reaction conditions, a wide range of alcohols, including simple aliphatic alcohols, allylic alcohol, propargyl alcohol, complex natural alcohols, and even water could all be applied to this three-component aminomethylation. "It is also impressive that this method can be used for the efficient linkage of two complicated drug candidates (Scheme 1, c)," said Professor Xing.

Professor Hu concluded: "This work offers an efficient electrophile-based asymmetric activation for aminomethylation with unstable formaldimine species. Further efforts to apply this protocol to the trapping of other types of active intermediates are ongoing in our labs."



Scheme 1 The electrophile-based asymmetric aminomethylation and its drug linkage application.

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Wenhao Hu received a B.S. in chemistry from Sichuan University (P. R. of China, 1987), M.S. from Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China, 1990), and Ph.D. from Hong Kong Polytechnic University (P. R. of China) with Professor Albert S. C. Chan (1998). He became a postdoctoral fellow at the University of Arizona (USA) with Professor Michael P. Doyle. In 2002-2006, he worked as a medicinal chemist at Genesoft in South San Francisco (USA) and a process chemist at Bristol-Myers Squibb in New Jersey (USA). In 2006 he joined East China Normal University (P. R. of China) as a professor of Chemistry, and the head of Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development. In 2016, he moved to Sun Yat-sen University (P. R. of China) as the head of School of Pharmaceutical Science. He received National Natural Science Funds for Distinguished Young Scholar (2011). His research interests include synthetic methodology, MCRs, and medicinal and process chemistry.

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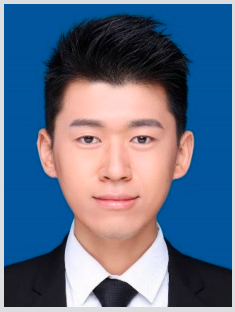

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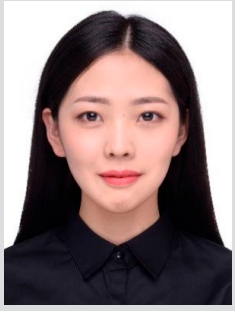

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