

Diels-Alder Cascades for the Synthesis of Fused N-Heterocycles

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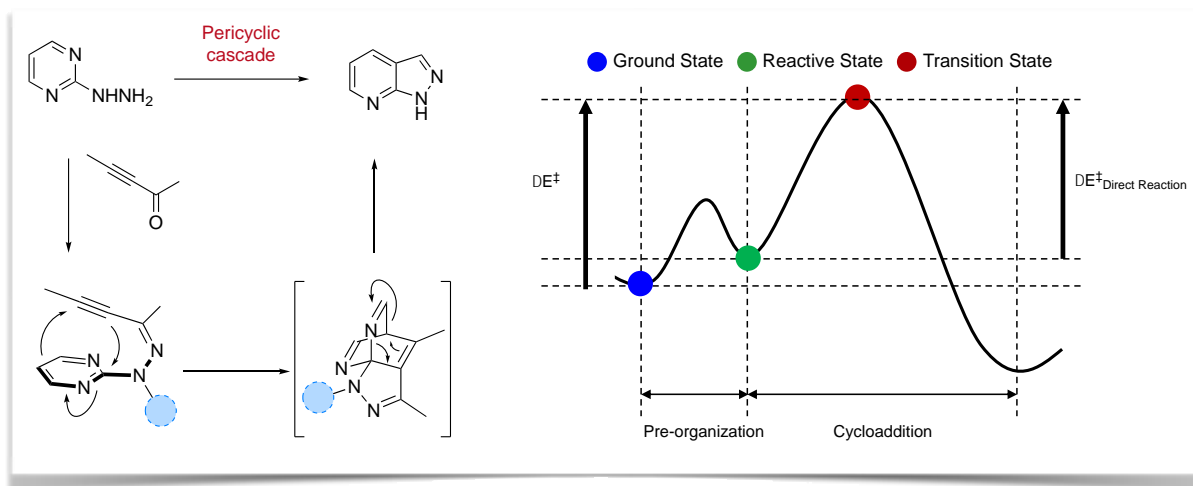
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Abstract:

Inverse electron demand Diels-Alder cycloadditions of azines are versatile tools to access chemical diversity. Among azines, pyrimidines are almost unreactive partners with dienophiles such as alkenes or alkynes and only reactions under drastic conditions have previously been reported. In line with our recent interest in pericyclic reactions,¹⁻³ we will discuss how 2-hydrazonylpyrimidines, easily obtained in two steps from commercially available 2-halopyrimidines, can be exceptionally activated by trifluoroacetylation. This allows a Diels-Alder cycloaddition under very mild reaction conditions, leading to a large diversity of *aza*-indazoles, a ubiquitous scaffold in medicinal chemistry.



This reaction is general and scalable and has an excellent functional group tolerance. A straightforward synthesis of a key intermediate of Bayer's Vericiguat illustrates the potential of this cycloaddition strategy. Quantum mechanical calculations show how the simple N-trifluoroacetylation of 2-hydrazonylpyrimidines distorts the substrate into a transition-state-like geometry that readily undergoes the intramolecular Diels-Alder cycloaddition.^{4,5}

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Nicolas studied chemistry at Paris 6 university and at the Ecole Normale Supérieure in Paris, France. He received his Ph.D. from the J. Cossy's laboratory in 2000, working with C. Meyer on the total synthesis of zincophorin. After postdoctoral studies with J.F. Normant (Paris 6 University, France) on carbometallation reactions and then with W. Roush (Michigan University, USA) on the total synthesis of formamycin, he joined the CNRS as a Junior Researcher in 2002. He became Directeur de Recherche in 2013 and is since then the head of the "Biomolecules, Synthesis and Methods" (BSM) team within the "Laboratoire d'Innovation Moléculaire et Application" (LIMA) (CNRS-Université de Haute-Alsace and Université de Strasbourg).

Nicolas received the "Advanced researcher award" of the French Chemical Society (2016), the "Syngenta Chemistry Lectureship" (2015), the "Guy Ourisson Award" (2014) and the "Bronze medal of the CNRS" (2012).

Representative publications:

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