

**Controlling non-enzymatic terpene cyclizations**

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Recent advances in iterative coupling methodologies and reaction automation have paved the way towards the fully automated synthesis of small organic molecules, however the synthesis of topologically complex molecules using such approaches remains a major challenge.<sup>1,2</sup> A potential answer to this challenge for complex terpenes could reside in the Tail-to-Head Terpene (THT) cyclization,<sup>3,4</sup> the reaction that gives rise to the majority of the topologically complex terpene structures encountered in nature. However, controlling the outcome of this reaction in the absence of the precisely structured active site of an enzyme has historically been very difficult. Here I will present a substrate-controlled approach to addressing this problem. Coupled with a predictive computer algorithm, this approach enables the predictable synthesis of a range of complex terpene structures from simple modular precursors, and could provide a pathway for the automated synthesis of terpenes through a linear-to-cyclized approach.

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[2] Daniel J. Blair et al., *Nature*, **2022**, 604, 92-97

[3] Qi Zhang, Konrad Tiefenbacher, *Nat. Chem.*, **2015**, 7, 197-202

[4] Qi Zhang, Jan Rinkel, Bernd Goldfuss, Jeroen S. Dickschat, Konrad Tiefenbacher, *Nat. Catal.*, **2018**, 1, 609-615