B. ABERLE, D. KOWALCZYK, S. MASSINI, A.-N. EGLER-KEMMERER, S. GERGEL, S. C. HAMMER, B. HAUER\* (UNIVERSITY OF STUTTGART, GERMANY) Methylation of Unactivated Alkenes with Engineered Methyltransferases to Generate Non-natural Terpenoids *Angew. Chem. Int. Ed.* **2023**, e202301601 DOI: 10.1002/anie.202301601.

## Engineered Methyltransferase-Catalyzed Terminal Prenyl Group Tail Methylation of Linear Terpenoids



Category

Organo- and Biocatalysis

## Key words

methylation

alkenes

terpenoids

methyltransferases

Synfact

**Significance:** Hauer and co-workers report an engineered methyltransferase-catalyzed methylation of terminal prenyl groups on the tail end of linear terpenoids. The methyltransferase selected for this transformation came from *Chlamydomonas reinhardtii* and was subjected to three rounds of sitesaturation mutagenesis in the optimization of the methylation of (*E*,*E*)-farnesol. In total, five terpenoids of various sizes were methylated with good to excellent conversions, all with complete chemoand regioselectivity. Methylation was observed in three more terpenoids. However, low conversion did not allow for isolation or structural determination of the corresponding products.

**Comment:** The selectivity for the terminal prenyl group of the reported reaction is remarkable and was thus far not achievable through small-molecule catalysis. The authors report that the obtained methylated non-natural terpenoids are optically active. However, the absolute configuration of the products and the enantioselectivity of the reactions were not determined (although the authors suggest (*S*)-selectivity based on the reactivity of sterol). Chirality is of vital importance when considering the potential bioactivity-related applications of these molecules, and we hope that the authors will examine these factors in potential follow-up studies.