Single-Step Enzymatic Synthesis of \( \beta \)-Methyltryptophans

**Significance:** Arnold and co-workers report an enzymatic single-step synthesis of \( \beta \)-methyltryptophan analogues from various nucleophiles and L-threonine by using a mutant \( \beta \)-subunit of the heteromeric tryptophan synthase from *Pyrococcus furiosus* (PtTrpB). This subunit, derived from directed evolution, proved to be significantly more active than the wild-type subunit.

**Comment:** By employing directed evolution, the authors have previously achieved the restoration of activity of the sole \( \beta \)-subunit of the heteromeric tryptophan synthase from *Pyrococcus furiosus*, which facilitates applications outside the cell ([Proc. Natl. Acad. Sci. U.S.A. 2015, 112, 14599]). The current work is an intriguing extension that permits the efficient transformation of threonine instead of serine. The resulting \( \beta \)-methyltryptophans are valuable precursors to a variety of natural products and could previously be only accessed by several chemical or enzymatic steps.

**Selected examples:**

- \( \text{Nu} = \text{HetAr, PhSH} \)
- \( \text{L-threonine (10 equiv)} \)
- \( \text{PLP (0.06–0.6 mol%) DMSO–aq KP buffer, 75 °C} \)

**Selected examples:**

- 8200 TTN 72% yield dr and er > 99:1
- 220 TTN 17% yield
- 500 TTN 33% yield
- 1300 TTN 14% yield (N-Boc derivative, over two steps)

\( \text{PfTrpB} = \beta \text{-subunit of tryptophan synthase from } \text{Pyrococcus furiosus} \)

\( \text{TTN} = \text{total turnover number} \)

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