Palladium-Catalyzed Synthesis of Cyclophane-Braced Peptide Macrocycles

Significance: Cyclic peptides possess great potential for modulating challenging biological processes. The authors have developed a general method for the synthesis of cyclophane-braced peptide macrocycles through palladium-catalyzed C(sp³)–H arylation.

Comment: Cyclophane motifs with unusual structural and stereochemical complexity were obtained by the picolinamide-directed intramolecular γ-selective C(sp³)–H arylation of the N-termini of peptide substrates at both the methyl and methylene positions.

Pd-catalyzed picolinamide-directed intramolecular C–H arylation of peptides:

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Selected examples:

61% yield (130 °C, 48 h)

24% yield

78% yield, dr > 20:1

75% yield, dr = 2:1

50% yield, dr = 1.5:1 (120 °C, 24 h)

51% yield, dr = 1.1:1 (120 °C, 24 h)