Palladium-Catalyzed C(sp³)–H Arylation of Cyclic Peptides

Significance: In medicinal chemistry and pharmaceutical research, late-stage modification of native peptides is a promising strategy for obtaining analogues that might have beneficial effects. In particular, modifications of cyclic peptides are important from the points of view of metabolic stability and cell permeability. The authors have developed a Pd-catalyzed C–H arylation method for the modification of cyclic peptides.

Comment: The authors have developed a method for the platinum-catalyzed C(sp³)–H functionalization of an internal alanine residue of a cyclic peptide, directed by an adjacent methionine residue. The C(sp³)–H arylation proceeds smoothly in moderate yields. Furthermore, the method permits the incorporation of bioactive functional groups into cyclic peptides.

Selected examples:

- 51% yield
- 35% yield
- 41% yield
- R = H, 26% yield
- Me, 55% yield

*Without AgOAc, and 20 mol% of Pd(OAc)₂ was used.

Pd(OAc)₂ (15 mol%)
AgOAc (1.5 equiv)
HFIP, 110 °C, 20–24 h