Palladium-Catalyzed Site-Selective \( \gamma\)-C(sp\(^3\))–H Silylation of Peptides

Selected examples: Pd-catalyzed \( \gamma\)-C(sp\(^3\))–H silylation of \( \alpha \)-amino acids:

Reaction conditions: 
Pd(OAc)\(_2\) (10 mol%) 
dichloro, (SiMe\(_3\))\(_2\) 
AgCO\(_3\), KHF\(_2\) 
DCE, 100 °C, 24 h

\( \gamma\)-TMS-Val-OMe 66% yield (m/d = 1.5:1)
\( \gamma\)-TMS-Ile-OMe 54% yield (m/d = 2.6:1)
\( \gamma\)-TMS-Thr-OMe 65% yield (m/d = 2.8:1)
\( \gamma\)-TMS-Thr-Pro-OMe 45% yield

Selected examples: Pd-catalyzed \( \gamma\)-C(sp\(^3\))–H silylation of dipeptides:

Reaction conditions: 
Pd(OAc)\(_2\) (10 mol%) 
2,6-DICBQ, (SiMe\(_3\))\(_2\) 
AgCO\(_3\), NaHCO\(_3\) 
PhMe, 120 °C, 24 h

\( \gamma\)-TMS-Val-Ile-OMe 69% yield (m/d = 1.5:1)
\( \gamma\)-TMS-Val-Tle-OMe 64% yield (m/d = 2.8:1)
\( \gamma\)-TMS-Ile-Pro-Tle-Ala-OMe 38% yield

Selected examples: Pd-catalyzed \( \gamma\)-C(sp\(^3\))–H silylation of tripeptides and tetrapeptides:

Reaction conditions: 
Pd(OAc)\(_2\) (15 mol%) 
2-CINQ, (SiMe\(_3\))\(_2\) 
AgCO\(_3\), NaHCO\(_3\) 
PhMe, 120 °C, 24 h

\( \gamma\)-TMS-Val-Tle-OMe, 65% yield (m/d = 2.4:1)
\( \gamma\)-TMS-Val-Tle-Val-OMe, 43% yield (m/d = 2.4:1)

Significance: Chemically modified unnatural peptides are often endowed with improved biological and pharmacokinetic properties and are therefore valuable in the drug-discovery process. Modification by silicon-containing groups appears to be promising, because the presence of a silicon moiety in amino acids or peptides can help to improve permeation through membranes and increase proteolytic stability.

Comment: Shi and co-workers have developed an efficient procedure for the synthesis of various \( \gamma\)-silyl-\( \alpha \)-amino acids and oligopeptides by palladium(II)-catalyzed \( \gamma\)-C(sp\(^3\))–H silylation. The present site-specific late-stage C(sp\(^3\))–H functionalization is assisted by a picolinamidine auxiliary and uses cheap and commercially available hexamethyldisilane as a silylating agent. Compatibility with a broad range of amino acid residues and the facile removal of the picolinamide auxiliary are noteworthy features of the present protocol.