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Improved Electrochemical Peptide Synthesis Enabled by Electron-Rich Triaryl Phosphines
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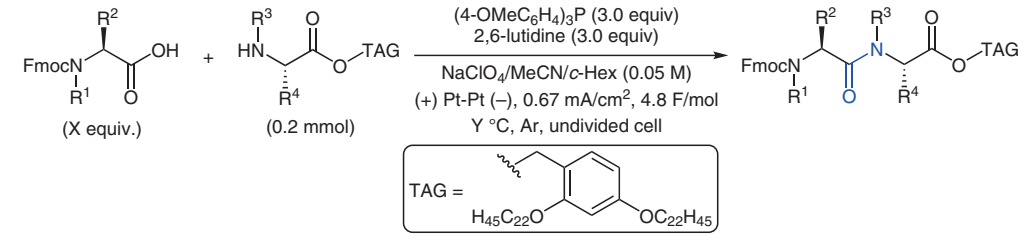
Electron-Rich Triaryl Phosphine Mediated Electrochemical Synthesis of Peptides

Electrochemical peptide synthesis:



applicable to sterically hindered amino acids
synthesis of oligopeptides including Pro-Pro residues

Substrate scope:

Fmoc-Pro-Asp(O*t*-Bu)-OTAG[a] 97% yield, dr > 20:1	Fmoc-Asp(O*t*-Bu)-Asp(O*t*-Bu)-OTAG[c] 97% yield, dr > 20:1	Fmoc-Sar-Asp(O*t*-Bu)-OTAG[d] 91% yield	Fmoc-Aib-Asp(O*t*-Bu)-OTAG[e] 99% yield
Fmoc-Pro-Pro-OTAG[a] 98% yield, dr > 20:1	Fmoc-Asp(O*t*-Bu)-Pro-OTAG[a] 91% yield, dr > 20:1	Fmoc-Sar-Pro-OTAG[a] 94% yield	Fmoc-Aib-Pro-OTAG[e] 96% yield
Fmoc-Pro-Aib-OTAG[a] 95% yield, er > 20:1	Fmoc-Asp(O*t*-Bu)-Aib-OTAG[b] 98% yield, er > 20:1	Fmoc-Sar-Aib-OTAG[b] 99% yield	Fmoc-Aib-Aib-OTAG[b] 80% yield
Fmoc-Pro-Sar-OTAG[a] 97% yield, er > 20:1	Fmoc-Asp(O*t*-Bu)-Sar-OTAG[b] 96% yield, er > 20:1	Fmoc-Sar-Sar-OTAG[d] 96% yield	Fmoc-Aib-Sar-OTAG[b] 83% yield
Fmoc-Pro-NMePhe-OTAG[b] 25% yield, dr > 20:1	Fmoc-Asp(O*t*-Bu)-NMePhe-OTAG[b] 63% yield, dr > 20:1	Fmoc-Sar-NMePhe-OTAG[b] 95% yield	Fmoc-Aib-NMePhe-OTAG[b] 0% yield

[a] Acid (2.0 equiv), r.t; [b] Acid (2.5 equiv), 60 °C; [c] Acid (1.5 equiv), r.t; [d] Acid (2.0 equiv), 60 °C; [e] Acid (2.5 equiv), r.t.

Significance: Electrochemical peptide synthesis received considerable attention in peptide chemistry. The authors reported the synthesis of peptides using electron-rich triaryl phosphine under electrochemical conditions. The methodology was examined for a broad range of substrates including oligopeptides.

Comment: The authors developed an improved electrochemical peptide synthesis method using an electron-rich triaryl phosphine that is effective for sterically hindered amino acids and challenging peptides like Rapastinel and Bradykinin. ^{18}O-Labeling experiments suggested the suppression of side reactions, by enabling efficient peptide coupling. This advancement will drive the development of novel peptide synthesis and more efficient synthetic systems for highly hindered amino acids.

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Category
Peptide Chemistry

Key words
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Synfact of the Month